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Dwarfism Associated with Microcephalic Idiocy and Renal Rickets

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IN RECENT years it has become increasingly evident that roentgen or radium irradiation of the pregnant female may endanger fetal development. There are now many case reports in evidence that intentional or accidental pelvic irradiation in therapeutic dosage may induce a variety of fetal anomalies, chief of which are microcephaly and idiocy. Most notable among these reports are those of Murphy (1, 2), Miller (3), Farber (4), Driesen (5), Doll (6), and Maxfield (7). All of these authors are quite emphatic in their advice to interrupt by some infallible means those pregnancies which have been complicated by pelvic irradiation. Taussig (8) sums up the situation very well as follows. "As the use of X-rays and radium in large doses for the treatment of cancer and myoma becomes more common, we are faced with a new indication for the interruption of pregnancy. The object here is not so much to help the mother as to prevent the birth of a microcephalic idiot or other monstrosity. The careful analysis of D. P. Murphy brings convincing evidence of serious fetal injury following a large proportion of cases that are subjected to extensive pelvic radiation during early pregnancy. Indeed, the fact of this injury is taken advantage of in the nonsurgical method of abortion by X-ray in early pregnancy. It is, therefore, claimed that whenever by mistake or necessity a pregnant uterus has been subjected to heavy radiation it is unwise to permit the child to continue development, as it is reasonably certain to turn out to be an idiot or deformed. This is one of the most positive of the eugenic indications and might perhaps be grouped under that head, although it has seemed to me a rather direct injury to the ovum. The concensus, however, is that if radium therapy of over 1500 milligram hours, or its equivalent in X-ray, has been applied to the pelvic organs within the first five months of gestation the assumption of serious fetal damage is so great that the pregnancy should be terminated."

CASE REPORT

The case reported seems to fall into such a category of 'radiogenic' microcephalic idiocy. The unusual aspects presented by this patient are the strikingly bizarre dwarfism and renal rickets as well as microcephalic idiocy. When four years of age the patient was reported by Amesse and Black (9) as an example of renal dwarfism. These observers were either misinformed by the patient's parents or were unimpressed

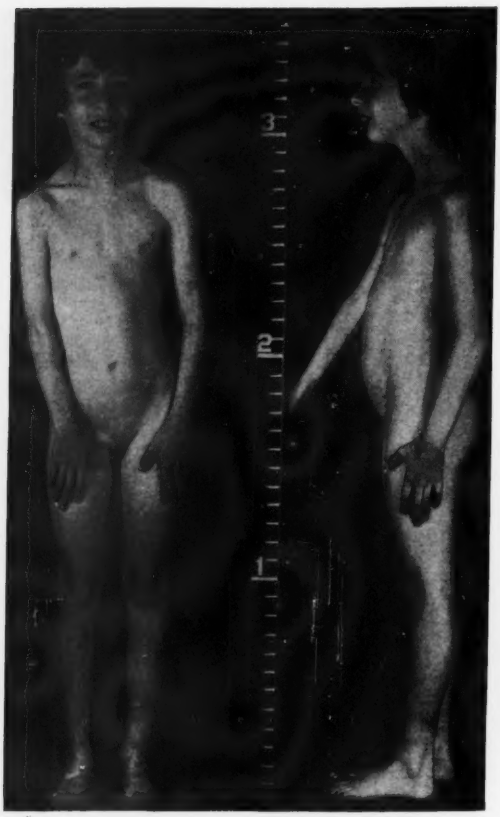

FIG. 1. The patient at age of 10 years.

by the pelvic irradiation sustained by the mother during the latter five months of her pregnancy. Only after the mother died of nephritis in 1938 was the story of the irradiation fully revealed to the author.

There are no other dwarfs or mental defectives in the family, the entire family being of average stature. The father and two older sisters are living and well. When the mother became pregnant she was suffering from inactive pulmonary tuberculosis and active tuberculous osteomyelitis of the sacro-iliac joint with a draining sinus. Because of preceding amenorrhea of about nine years' duration she was unaware of the pregnancy until about the third month. She then requested a therapeutic abortion. This was attempted by roentgen irradiation of the pelvis which failed to achieve the desired result. However, the irradiation was persistently carried on at weekly intervals from the third to the eighth month. The pregnancy was finally terminated in the eighth month by caesarean section. The fetus was still alive and weighed two and three-fourth pounds. The weight soon dropped to one and a half pounds. Life was maintained with great difficulty by artificial feeding. During the first two years there were convulsive seizures suggestive of rickets. Somato-psychic development was extremely slow. Dentition began at about one year and walking at about three years of age. Enuresis persisted until the child was about four years old. She remained remarkably free from the usual exanthemata of childhood. There were rare, mild, sore throats. Dwarfism and imbecility became apparent in infancy and continued throughout the life of the patient. However, some growth and general development were achieved during the last five years of the present observation.

At seven and one half years of age, when first seen by me, the patient's height was 38 inches, weight 23¾ pounds and her I.Q. (Stanford-Binet) about 30. The bizarre, wizened, senile, mousy appearance of the patient is not well conveyed by the accompanying photographs. The body was symmetrically dwarfed, slender, hypoplastic and very poorly nourished. There was a striking lack of subcutaneous fat. The skin was dry and clear except for some widely scattered small pigmented macules. There was a minor scoliosis. The skull was small. The eyes were small but in proportion to the dwarfed body. The front upper teeth were large and protruded so that they overlapped those of a receding lower jaw. Fetor oris was frequently noted. Throat and lungs were clear. Heart action was normal. The blood pressure fluctuated between 105/70 to 120/75. There was no lymphadenopathy. Muscular coordination was of low order. The walking gait was uncertain and rather clumsy. Tendon reflexes were slightly hyperactive. The patient was up and about, playing simple childish games, conversing cheerfully on a level of a two to three year old child. The vocabulary was extremely limited. Dressing was accomplished with dif-

TABLE I. BLOOD CHEMISTRY

Date	6/37	10/38	4/39	10/39	4/40	2/41
	mg.%	mg.%	mg.%	mg.%	mg.%	mg.%
Sugar	95					121
Cholesterol	238					390
Urea		59	50			
N.P.N.	51	70	84	78	100	108
Creatinine		2.6	2.0	3.4	2.1	2.5
Calcium	10.2	11.4	10.5	11.4	10	9.9
Phosphorus	4.3	5.1	6.0	6.1	7	7.4
Serum Albumin	4.2	6.7	4.1			
Globulin	2.4	1.3	2.2			
Phosphatase (Bodansky units)		8.2	9.1		10.8	12

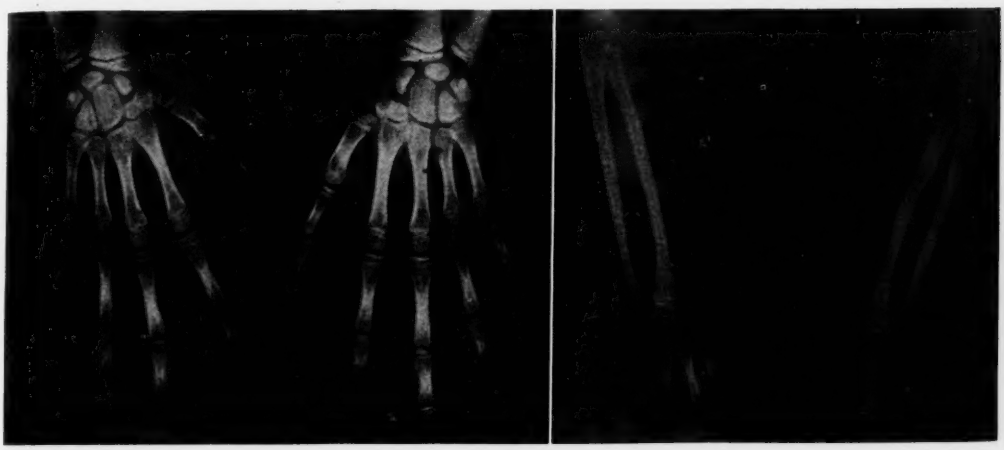

FIG. 2. Wrist and forearm of patient at age 10. Bone age, normal.

ficulty. A limited mixed diet with vitamin supplement was accepted. Bladder and bowel control was established at this time. The patient remained uniformly uncomplaining, though a limited intelligence may not have appreciated discomfort even if present.

LABORATORY DATA: Repeated urinalysis revealed constant heavy albuminuria with a range of specific gravity of 1010–1016; pus cells were always and casts infrequently present; erythrocytes were rarely seen; no cystine crystals were present; urine creatine was 38 mgm. in 24 hours.

There was a constant hypochromic anemia. The initial blood count (June 23, 1937) showed: hemoglobin 57 per cent (Sahli), erythrocytes 3,270,000, leucocytes 8200 with a normal differential count except for 6 per cent eosinophiles. The blood count improved following an optimum diet supplemented with iron so that a hemoglobin of 78 per cent and erythrocytes

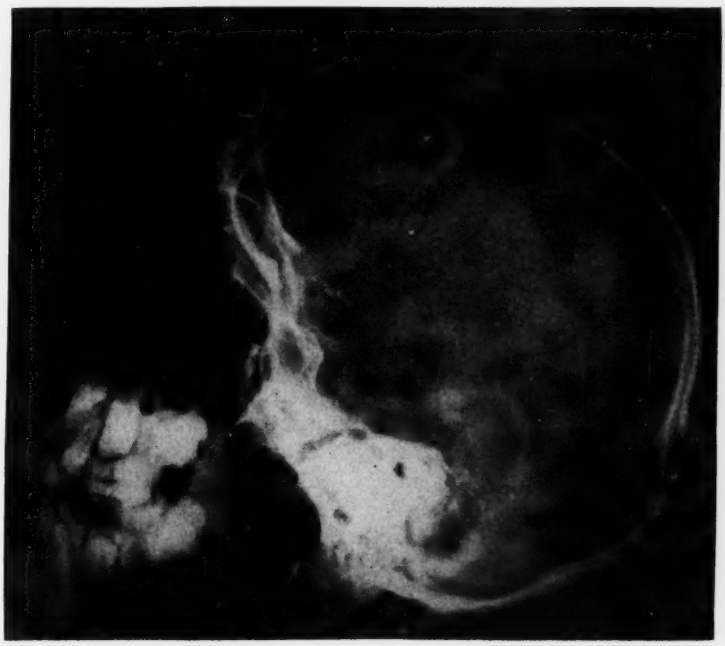

FIG. 3. Skull plate of patient, age 10. Sella turcica, normal; anterior fontanel, open.

of 4,320,000 were attained. However, the progressive azotemia soon reduced the blood counts down to a hemoglobin of 49 per cent (Sahli) and erythrocytes of 3,030,000.

Roentgenograms of the skull and arms are shown in the accompanying photographs. There was no deformity, nor any decalcification of the bones. No radiographic evidence of rickets was observed up to September 24, 1941 after which no more radiographs were taken. The 'bone age' appeared to be normal.

Intravenous urography showed small kidneys without any significant distortion.

TREATMENT

Treatment of the patient was entirely symptomatic. Thyroid and growth hormones were administered in moderate doses to attempt stimulation of growth and intelligence. Results were difficult to evaluate. Within the five years period of observation there was an increase of almost 10 inches in height and about 19 pounds in weight. There was a definite improvement of intelligence as measured by the I.Q., rising from about 30 to 60, but the patient never rose above the state of imbecility. In her thirteenth year some secondary sex characters began to appear, i.e., a few sparse pubic hairs and a slight mammary growth. Throughout observation there were occasional episodes of nausea and vomiting associated with sluggish behavior. This was apparently due to a chronic azotemia with infrequent bouts of uremia. Nitrogen retention fluctuated considerably. During the last ten months of her life the patient resided at the County Poor Farm. Here she developed an otitis media which apparently cleared up uneventfully; but a recurrence of the infection was complicated by mastoiditis which was refractory to sulfonamide therapy. The infection extended into the cranial cavity and the patient died of a septic meningitis on May 27th, 1942.

AUTOPSY FINDINGS

Since the patient died at a County nursing home, the post-mortem examination was made by Dr. H. A. Edmondson of the Los Angeles County Hospital. This anatomical summary will be limited to the important positive and negative findings.

General. The body was that of a slender, poorly nourished and developed white female weighing 29.5 kgm., and measuring 120 cm. in height. There is some disproportion between the size of the head and length of the body, the head being rather small. The breasts and external genitalia were poorly developed. A purulent discharge was noted in the left external auditory canal.

Urogenital system. Examination of the urogenital system revealed rather striking changes. The kidneys were extremely small and together weighed 60 gm. The capsules stripped with difficulty causing lacerations of the parenchyma. The external surface showed considerable discreet and confluent areas of scarring. The cortex was extremely thin, measuring from 1 to 2 mm. in thickness. The pyramids were indistinct. The pelves and calices were slightly dilated, filled with cloudy urine and the walls moderately thickened and edematous. The ureters and urinary bladder were not remarkable.

Microscopic examination of the kidneys revealed marked atrophy of the parenchyma. The arteries were relatively free from sclerosis, only an occasional one showing slight to moderate thickening of the wall with intimal sclerosis. An occasional glomerulus was completely or partially hyalinized; some were congested, and some presented hyaline thrombi. Many of the convoluted and collecting tubules were dilated and some contained granular and hyaline casts. The interstitial tissue was moderately increased throughout the areas of atrophy. The tubules in these areas were atrophic. Moderate round cell infiltration and a few polynuclear cells were seen in the stroma.

The internal genitalia were poorly developed. The ovary, uterine tubes and uterus were infantile in appearance. On microscopic examination the ova were relatively few in number, but the stroma was not remarkable. The endometrium was relatively hypoplastic but the myometrium was not remarkable.

Central nervous system. Examination of the central nervous system was performed by Dr. C. B. Courville as well as Dr. Edmondson. The dura mater was normal except for a small amount of extradural purulent exudate in the left temporal region. At this point the inner table of the cranium was completely destroyed by a necrotic purulent osteomyelitis which apparently had extended from the mastoid and

middle ear into the squamous portion of the temporal bone. Examination of the ear revealed the drum membrane to be absent and the middle ear and mastoid air cells filled with purulent exudate. The veins and blood sinuses about the area were not involved. The brain was rather small. It measured 12.9 cm. in the longitudinal diameter, 10.1 cm. in its transverse diameter and 8.2 cm. in its vertical diameter. The frontal convolutions were more or less direct, simple, single convolutions representing the superior, middle and inferior frontal gyri. The temporal convolutions seemed to extend well back into the occipital area and where normally a number of small gyri exist, there were about three distinct gyri occupying the dorsal surface of the occipital lobes. The cranial nerves, as far as they could be traced, seemed to be normal. An abscess was noted in the right frontal lobe of the brain which communicated with the sub-arachnoid space through a hiatus at the base of the brain of about 1 cm. in diameter. There was considerable purulent exudate in the soft meninges of the brain extending into the arachnoid of the Sylvian fissures on both sides. The cerebellar gyri were somewhat "warty" in appearance, but in general were not remarkable. There was considerable purulent exudate over the dorsal surface of the cerebellum.

Repeated coronal sections of the brain revealed an area of necrosis (the abscess noted above) in the lateral inferior aspect of the right frontal lobe involving the cortex and underlying centrum. The section passing through the posterior portion of the posterior capsule disclosed an area of necrosis in the upper portion of the centrum of the right parietal lobe measuring .5×.8 cm. Repeated section through the remainder of the brain and brain stem revealed nothing remarkable except for rather small cerebellar folia.

Microscopic examination of the brain revealed infiltration of the soft meninges by leucocytes. Underlying the area of inflammation the parenchyma showed evidence of a recent abscess. The cortex of the brain was somewhat acellular in certain areas, chiefly in the superficial zones. The nerve cells were in part somewhat sclerotic and a few were definitely degenerated. The white matter appeared somewhat condensed and the oligodendroglia swollen. Sections stained with the cyanide method confirmed the impression that the nerve cells were rather small and showed a tendency to be sclerosed. There was also a tendency for the nerve cells to be disoriented so far as their axes were concerned. The large Betz cells seemed to be normal in most respects.

Sections stained with the gold sublimate method showed a generally normal number and distribution of astrocytes, except in the cortex, where they seemed to be increased in number and transformed into the fibrous type. This suggests some form of focal degenerative change. Sections stained with the Bielschowsky method showed that the nerve fibres of the cortex were relatively unaltered. Sections with the myelin sheath stain showed degeneration in the region of the abscess. Sections through the frontal region with the same stain showed small collections of myelinated fibres approximately at the spot where the olfactory tract should be. Sections from the cerebellum showed some variability of the granular cell layer, but other than this, nothing remarkable was seen.

Endocrine system. Examination of the endocrine system revealed significant findings only in the parathyroids and in the ovaries. The left inferior parathyroid gland was moderately enlarged, measured 1×6×3 cm. and was definitely hyperplastic. The other three parathyroid glands were small. Sections of the parathyroid gland revealed an adenomatous hyperplasia of the chief cells with only small irregular nests of oxyphil cells. In only an occasional area was differentiation into acini noted. In one of the sections the adenomatous hyperplasia was characterized by pronounced differentiation into large acini with tall columnar epithelium. The ovaries were very hypoplastic, revealing only a few ova on microscopic section. Gross and microscopic examination of the pituitary gland, suprarenal gland, thyroid gland and thymus revealed nothing remarkable.

Cardio-vascular system. The cardio-vascular system revealed no appreciable abnormality.

Respiratory system. The respiratory system revealed nothing remarkable except for areas of broncho-pneumonia.

Skeletal and Muscular systems. Examination

of the skeletal and muscular systems revealed an unusual density of the bodies of the vertebrae and beading of the ribs in the epiphysis and in the diaphysis. Sections of the rib taken from the epiphyseal line disclosed an irregular line of ossification composed of groups of cartilage cells with interspersed islands of ossification and fibrotic areas. The marrow spaces of the diaphysis were filled with fibrotic and fatty marrow. Only a few islands of hematopoiesis were seen. Section of the vertebra revealed a distortion of the normal trabecular pattern by areas of incomplete ossification and masses of calcified cartilage. There were areas of osteoid tissue formation without evidence of osteocytes.

Anatomical Diagnoses.

1. Dwarfism.
2. Hypoplasia of the internal and external genitalia.
3. Hypoplasia of the breasts.
4. Hypoplasia of the brain.
5. Pyelonephritis with renal rickets.
6. Adenomatous hyperplasia of one parathyroid gland.
7. Atrophy of the bone marrow with areas of fibrosis.
8. Irregular ossification of cartilaginous bones.
9. Acute purulent otitis media and mastoiditis.
10. Osteomyelitis of the skull with extension into the cranial cavity.
11. Acute purulent pachy-meningitis and lepto-meningitis.
12. Brain abscess.
13. Terminal broncho-pneumonia.

DISCUSSION

It is difficult to ascribe this clinical syndrome to any category other than to one induced by prolonged intensive roentgen irradiation during intra-uterine life. Without definite knowledge of the dosage of the roentgen irradiation sustained by the growing fetus during the latter five months of pregnancy, the degree of fetal damage must be speculative. The failure of the given radiation to induce fetal death or abortion does not militate against the probability that even sublethal irradiation, if prolonged enough, will impair fetal development. It seems most unlikely that a weekly pelvic irradiation for five months will be without effect on a growing embryo. The fact that the therapeutic abortion was not attempted until approximately the third month of pregnancy provides another reason for fetal survival. A three-month-old fetus would be much less radiosensitive than a younger embryo. According to Johnson (10) the earlier in pregnancy the radiation is given and the higher the dosage of the irradiation the greater is the injury to the growing fetus. Driesen (5) concluded that exposures to radium or roentgen radiation in the first half of pregnancy may induce abortion, while in the latter half pregnancy is not terminated but the newborn infants are apt to be subnormal in some way.

The post-mortem findings of abnormal epiphyseal architecture in association with chronic pyelonephritis and some parathyroid hyperplasia make the diagnosis of renal rickets fairly obvious. The rickets and the parathyroid hypertrophy are considered to be secondary to the pyelonephritis, and due to the renal failure to excrete phosphorus. One may speculate that the rickets may have been a factor in the dwarfism. It must be noted, however, that in classical examples of renal dwarfism the mineral disturbance and bony deformity are usually quite extensive. In the present instance the abnormal serum calcium and phosphorus values are relatively minimal in degree and appear late in the stage of kidney failure. It must also be noted that up until November, 1941, there was no roentgen evidence of rickets being present and no obvious rickets was ever observed clinically. Even though the clinical evidence of renal rickets is not very striking, one must ascribe some importance to the renal lesion in the production of the dwarfism. How much of a role the irradiation played in the production of the somato-psychic hypoplasia is difficult to evaluate. So much depends on knowing what x-ray dosage was actually used in the five months of irradiation of the pregnant mother. The clinical and experimental observations of Murphy (2, 11) leave no doubt as to the damage wrought on the growing fetus by such irradiation. Dwarfism of the experimental animal is readily induced. The unusual aspects of the case under discussion were probably due

to the particular time sequence when the irradiation was applied, as well as to the existence of renal rickets. The degree to which each of these noxious agents contributed to the dwarfism remains speculative. Their influence on endocrine function is likewise difficult to evaluate. With the exception of the ovarian hypoplasia and the compensatory hyperplasia of the parathyroids the other endocrine glands were relatively intact. However, the histologically normal structure of the pituitary, thyroid and adrenal glands does not necessarily imply normal hormonal activity. Furthermore it may be reasonable to speculate that the cerebral hypoplasia deprived the pituitary and related endocrine glands of the normal integrating activity of the important hypothalamus. Cushing (12), Riddoch (13), Brooks (14) and others have emphasized the importance of the hypothalamico-hypophyseal mechanisms in the smooth metamorphosis and functioning of the entire human economy. In other words normal somato-psychic development may be incompatible with cerebral hypoplasia.

Thus both renal rickets and cerebral hypoplasia constitute the most probable pathogenesis of the clinical syndrome under consideration. However, the neurological defect may have been the dominant lesion.

SUMMARY

This report is concerned with a case of bizarre dwarfism associated with microcephalic idiocy and renal rickets. The child was born following irradiation of the maternal pelvis for a period of five months and died in the 13th year from an intercurrent infection. At autopsy extreme nervous and somatic hypoplasia was seen. This is considered to have been the result of brain damage induced by the roentgen irradiation and renal rickets.

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Excretion of Estrogen After the Injection of Estradiol and Estrone into Men with Cirrhosis of the Liver

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NUMEROUS observations on laboratory animals (1, 2, 3,), as well as on human subjects (4, 5) have now established the fact that the liver plays a dominant rôle in the metabolism of estrogens. However, the nature of this function of the liver is not well understood.

The data of experiments on human male subjects indicate that, after intramuscular injections of large doses of estrogens, so much of the hormone is lost in the process of intermediate metabolism that relatively small portions are recoverable in the urine. This major loss of estrogenic activity is variously ascribed to mechanisms of destruction, inactivation or conversion by the liver.

Thus far the fate of injected estrogens have been observed only in normal male subjects. Heard and Hoffman (4) recovered in the urine of a young man 16.2 mg. estrone and 9.8 mg. of estradiol after the intramuscular administration of 250 mg. of estradiol injected over a period of 8 days. This indicates a recovery of only 10% of the activity. Pincus and his co-workers (6, 7) have likewise recovered low yields of estrogens after injecting normal young males with estrone and estradiol. For example, Schiller and Pincus (7) reported that a young man injected with a single intramuscular dose of 21.6 mg. estradiol excreted 1% estradiol, 2.7% estrone and 5.4% estriol in a 6-day collection of urine. This indicated that injected estrogens lose much of their activity in the presence of normal liver function. Liver damage has been shown radically to alter the metabolism of estrogens. When the liver is subjected to sublethal poisoning with carbon tetrachloride, estrogenic effects are accentuated. For example, Pincus and Martin (8) demonstrated that after such liver damage the effectiveness of injected estrogen in spayed rats was enhanced about 80%. Comparable effects may be seen in human subjects who manifest liver failure incident to far advanced hepatic cirrhosis. We now believe that such livers are no longer able to inactivate endogenous estrogens. The evidence of two previous reports (5, 9) indicated that males with advanced liver cirrhosis excreted urinary estrogens in free rather than in combined form. The gynecomastia and testicular atrophy, noted in the majority of these cases, may therefore be ascribed to circulating free estrogens.

In line with the above experimental and clinical observations one may expect that estrogens injected into men with hepatic cirrhosis would be excreted in higher concentrations than in normal males. Such appears to be the case. The results of injecting estrogens[1]

[1] To Roche-Organon, Inc. and Ciba Pharmaceutical Products, Inc. we extend thanks for the estrone (Menformon) and estradiol diproprionate (Di-Ovocylin).

into four men with liver failure (because of Laennec's cirrhosis) are here reported. Since our main objective was to determine the total estrogen excretion after their injection, no attempt was made to identify nor isolate specific estrogens in the urine.

The four male subjects were hospitalized on account of advanced hepatic cirrhosis associated with clinical evidence of liver insufficiency manifested chiefly by ascites (requiring repeated paracentesis) and anemia incident to bleeding from rectal or esophageal varices.

METHODS[2]

The estrogen and 17-ketosteroid values were determined on 24-hour urine specimens before the injection of the estrogens. Following the injections, assays were carried out on urine specimens collected for 7–11 days.

After prompt extraction in carbon tetrachloride, estrogens were assayed on spayed rats. By our assay method 1 R.U. = 10 I.U.

After the injection the 17-ketosteroid values were determined on only two of the subjects by the method of Neustadt (10) using the Evelyn photoelectric colorimeter. The total or combined fractions of estrogen and 17-ketosteroids were recovered from specimens which were subjected to acid hydrolysis (12 hours for the estrogen and 15 minutes for the 17-ketosteroids).

The "free" estrogens were recovered by the omission of the usual acid hydrolysis prior to extraction with carbon tetrachloride.

Each specimen was therefore divided into four aliquots, two of which were assayed for the combined and the other two for the free fractions.

We are as yet unaware of the significance of so-called free and combined fractions of the 17-ketosteroids but their separation was deemed advisable for uniform treatment of the problem. Subject A. (G. A.), age 61, was injected with 600,000 I.U. estradiol diproprionate in two daily doses. Urine was then collected for 7 days and the estrogen assay of each 24-hour output is here tabulated. Subject B. (R. N.), age 63, was injected with 150,000 I.U. estrone in two daily doses. The urine was collected for 11 days and assayed in pooled lots of 48, 72, 72, and 72 hours respectively. Subject C. (D. M.), age 72, was injected with 20,000 I.U. estrone in a single dose. The urine was collected for 11 days, pooled and assayed in lots of 48, 72, 72 and 72 hours respectively. Subject F. (H. R.), age 29, was injected with 300,000 I.U. estradiol diproprionate in two daily doses. Urine was collected for 7 days and each 24- hour specimen was extracted separately. Only the first 24-hour specimen was assayed. The other extracts were lost.

RESULTS AND DISCUSSION

The data are presented in two tables and a graph. The latter depicts the excretion values of estrogens after injection of estrogens as compared with the data of controls.

Apparently high concentrations of the injected estrogen are recoverable in the urine of all these subjects. The proportion of free to combined fractions of estrogens is very small in subjects A, B and C. In subject F the reverse is true, the ratio of free to combined estrogen being 5:1 in the first 24 hours of urine after injection. Note also the high pre-injection control values in this subject. There is a curious uniformity of the post-injection values in subjects A and B. Subject A excreted essentially the same amount of both free and combined hormone fractions for the six consecutive days following the first day's rather large output. Here a longer post-injection collection period of urine may have yielded a more complete recovery of estrogen, even though the percentage yield seemed high enough.

The clinical effects of the injected estrogen were manifested in the breasts and prostates of all the subjects.

Subject F, with striking preexisting gynecomastia, developed acute painful hypertrophy of the breasts and transient urinary retention. This exaggerated response to estrogens may have been more marked in this subject because of the high pre-injection values of estrogens. It must be noted that the majority of males with advanced hepatic cirrhosis develop spontaneously varied degrees of gynecomastia and testicular atrophy (5, 9, 11).

It was thought that it might be interesting to observe the influence of injecting estrogens

[2] We are grateful to H. Hess and H. Bergman for technical assistance.

TABLE I. URINARY ESTROGEN VALUES AFTER INJECTION OF ESTRADIOL AND ESTRONE

Subject	A estrad. diprop. 600,000 I.U.		B[1] estrone 150,000 I.U.		C[1] estrone 20,000 I.U.		F estrad. diprop. 300,000 I.U.	
	combined	free	combined	free	combined	free	combined	free
	I.U.	I.U.	I.U.	I.U.	I U.	I.U.	I.U.	I.U.
Control	30	0	100	75			350	100
Days								
1	130,000	500					10,000	50,000
2	66,000	250	30,000	500	4,000	1,000		
3	66,000	250						
4	66,000	250						
5	62,000	250	30,000	200	12,000	1,500		
6	62,000	250						
7	62,000	250						
8			45,000	750	300	150		
9								
10								
11			22,500	150	300	150		
total	514,000	2,000	127,500	1,600	16,600	2,800	10,000	50,000
%	86.0		85.0		83.0		24 hour specimen only	

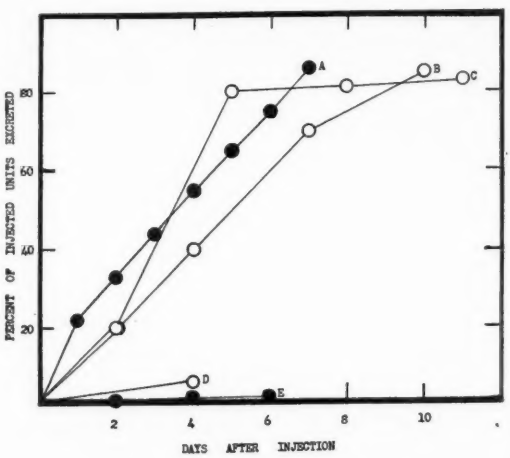
[1] Values of Subjects B and C represent pooled specimens of 48, 72, 72, and 72 hours respectively.

on the excretion of 17-ketosteroids. In subjects B and C the 17-ketosteroid values are not particularly significant; the hydrolyzed (combined) and unhydrolyzed (free) fractions were about evenly divided. The significance of these findings is not apparent.

The strikingly high values (83–86%) of estrogen recovered are in sharp contrast to those reported by Heard and Hoffman (4), and by Schiller and Pincus (6) in normal subjects. It is also interesting to note the abnormally high values of free and combined estrogens before injection, especially in subjects B and F. In our opinion this is further evidence of liver insufficiency. The bulk of the estrogen excreted is in combined form except in the case of subject F whose urine yielded largely free estrogen.

TABLE II. 17-KETOSTEROID VALUES AFTER THE INJECTION OF ESTROGENS

Subject B	Hydrolyzed (combined) mg.	Unhydrolyzed (free) mg.
Control	1.3	4.3
Day 1+2	10.0	3.7
Day 3+4	2.9	2.7
Day 5+6+7	4.2	3.5
Day 8+9+10	5.1	3.0
Subject C		
Control	4.1	3.7
Day 1+2	9.3	2.9
Day 3+4+5	6.7	7.6
Day 6+7+8	13.2	9.6
Day 9+10+11	11.8	4.8



Subject A injected with 600,000 I.U. estrone (free)
Subject B and C injected with 150,000 and 20,000 I.U. estradiol diproprionate respectively.
D and E represent composite data on normal subjects reported by Schiller and Pincus [(7) and Pearlman and Pincus (6) respectively.
D depicts urinary estrogen values after injecting a normal young man with 21.6 mg. estradiol (free).
E depicts urinary estrogen values after injecting 7 normal young men with estrone.

The latter subject undoubtedly had a more advanced degree of liver failure of which he subsequently died several months after the completion of the experiment. Hence it appears that the greater the liver damage, the greater is the failure to inactivate or convert the endogenous as well as the exogenous estrogen. However, it seems apparent that, even though the liver does not convert or destroy the injected estrogens, conjugation of the hormone is still in evidence. This ability to conjugate estrogen indicates some residual hepatic efficiency in subjects B and C in contrast to the almost total failure in subject F. The character of the excretion curves was essentially the same in subjects A, B and C regardless of whether estrone or estradiol was injected in free or esterified form.

The relative constancy of the estrogen values in the post-injection specimens of subjects A and B would suggest the possibility of a certain threshold mechanism. Uniform absorption from the site of injection may partially account for this but a kidney threshold must also be considered as a possible explanation.

SUMMARY

Urinary estrogens and the 17-ketosteroids were determined after injecting estrone or estradiol into four men with hepatic cirrhosis. Total excretion values in three subjects ranged from 83 to 86% of the injected dose. The bulk of the estrogen was in combined form, the free fraction constituting 1 to 14% in these three men. The fourth subject excreted mainly free estrogen hence liver failure was considered more complete than in the other cases.

There was a suggestion of a threshold mechanism in the excretion of high concentrations of circulating estrogens in two subjects.

The significance of the 17-ketosteroid values obtained is not apparent at this time.

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Some Metabolic Effects of Thiouracil with Particular Consideration of Adrenal Functions

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IT HAS BEEN demonstrated that thiouracil exerts a marked effect on the thyroid gland of rats (1) and man (2, 3). Thyrotoxic subjects receiving treatment with this drug experience a remission of the clinical manifestations of their disease together with a return to normal of the basal oxygen consumption and of the protein-bound iodine content of the plasma. However, the effects of this drug on the other tissues of the body have not been fully studied.

In certain patients described below, during the course of investigating the action of thiouracil given in daily dosages of about one gram, we have made a few observations suggesting that the effect of this drug on the adrenals should be carefully examined. (a) When thiouracil was administered for a few days or weeks to ten patients with diseases of such severity as to make death seem likely, the post-mortem estimation of the content of this substance in the various tissues revealed a higher concentration in the adrenals than in most of the other tissues (4). (b) In a few thyrotoxic patients receiving this drug, subcutaneous edema developed in spite of a normal serum protein, normal cardiac function and absence of demonstrable kidney damage, although they exhibited hyperchloremia (3). (c) One patient with the adrenal type of diabetes mellitus showed a marked reduction in glycosuria in association with thiouracil treatment but the poor dietary regulations made it advisable to study this effect under better controlled conditions.

Our studies of the effect of thiouracil on the adrenals have been directed chiefly along three lines: (1) macroscopic and microscopic alterations found post-mortem in the adrenal glands of rats and patients gravely ill of non-thyroid conditions; (2) the effect of this drug on the clinical manifestations of presumed hyperadrenocorticism; (3) the changes in certain constituents of the blood and urine which are affected, at least in part, by the function of the adrenals. The first 2 lines of attack have been considered (5, 6) and the third forms the basis of this paper.

METHOD OF STUDY

Six adult individuals, one normal and five with manifestations of hyperadrenocorticism,[3] were placed on a special ward for study. Two of these patients had diabetes mellitus, two had hypertension, one had slight impairment of

[1] This investigation was aided by a grant from the Milton Fund of Harvard University.

[2] Fellow of the Commonwealth Fund.

[3] Of the 5 patients designated as manifesting hyperadrenocorticism, one was a man who in addition to obesity and weakness had diabetes with a response to a glucose-insulin tolerance test similar to that found in the adrenal type of diabetes (20). Four females also exhibited a similar response to a glucose-insulin test and suffered from an appreciable amount of hirsutism and weakness. There was no evidence of primary ovarian disease.

kidney function and one had heptomegaly without impairment of liver function, as measured by the bromsulphthalein test. The general health of all the subjects was relatively good and no patient was confined to bed during the period of study. Each subject was placed on a constant diet, the chief constituents of which are given in the legends, and a few days later collection of all urine specimens was begun using 10 cc. of glacial acetic acid daily as a preservative. Each patient ate all of the allotted diet. Water was permitted as desired. In 2 cases free access to salt was given, but the average daily consumption was estimated by frequent weighings of the saltcellar. The other 4 patients were given 4 gm. of sodium chloride daily in addition to what was present in the food. In all but one case the above regimen was maintained for 40 to 48 days. This interval was divided into periods of 8 days each. All of the urine collected during this time was pooled and an aliquot taken for the various analyses described below. During the first period no treatment was given, but during the next 2 or 3 periods each patient received from 0.6 to 1.0 gm. of thiouracil, daily, in doses of 0.2 gm. In 5 cases the collection of urine was extended for 2 periods after cessation of treatment. Determinations were made of the average daily excretion in the urine of sodium,[4] chloride, potassium, nitrogen, creatinine and creatine. Estimations of the serum chloride, sodium, potassium, carbon dioxide combining power, and total protein were made before, during and after treatment. Glucose-insulin tolerance tests and determinations of the quantity of 17-ketosteroids excreted in the urine were conducted before, during and after treatment. The blood pressure and the strength, as measured by a hand dynamometer, were recorded daily. The basal oxygen consumption was determined in 5 cases preceding treatment and in 4 cases immediately following treatment. Changes in the degree of hirsutism were looked for.

[4] The methods used for the analyses are as follows: sodium, Butler and Tuthill (7) as modified by Consolazio and Dill (8); urine chloride, Wilson and Ball (9); plasma chloride Keys (10); potassium, Shohl and Bennett (11), as modified by Consolazio and Talbott (12); nitrogen, Gunning (13) and Arnold and Wedemeyer (14); creatine and creatinine, Folin and Wu (15); 17-ketosteroids, Talbot, Butler and Maclachlan (16); total serum protein, Kagan (17); sugar, Folin and Wu (18); carbon dioxide combining power, VanSlyke and Cullen (19); glucose-insulin tolerance test, Fraser, Albright and Smith (20).

RESULTS OF STUDY

The effect of thiouracil on the functions related to the adrenal may be conveniently considered under three headings: (1) salt and water metabolism; (2) androgenic effects; and (3) gluconeogenesis. However, it is to be emphasized that these hormonal effects are not strictly separate. It is also pointed out that the effects on the adrenal, if present, may not manifest themselves immediately and may possibly persist for many days after the discontinuation of thiouracil.

(1) *Salt and Water Metabolism.* (a) *Urine studies.* In 3 patients (M. C., M. O. and K. I.) there was a distinct increase in the amount of urine excreted both during and following treatment. In 2 others (M. E. and M. A.) there was a decreased excretion and in one (M. I.) there was no definite effect. There was no retention of sodium in patient M. O. (fig. 1), but in the other 5 patients there was some retention either during or following treatment. In patients M. I. and M. A. (fig. 2 and 3) the retention of sodium was striking, being associated with edema in M. A. In M. I. and M. E. (fig. 2) moderate retention of chloride existed during and following treatment. In M. O. and K. I. (fig .1) there was an increased elimination of chloride during treatment but a decrease thereafter. No definite effect was observed in M. C. (fig. 3). The amount of potassium excreted remained constant in M. O. and K. I. while in M. E. and M. A. it decreased with thiouracil treatment. In patient M. I. there was an increased elimination of potassium during therapy. (b) *Serum Studies.* Determinations of various constituents of the serum which affect water balance were conducted not only upon the 6 subjects described above but also upon some thyrotoxic patients and others receiving thiouracil treatment, there being 16 subjects in all. Seven of these patients were selected for study because of the appearance of edema during treatment. The values in all cases were normal either before treatment or within about one week after either cessation of treatment or marked reduction in the dosage. In no case was there heart failure or more than minimal kidney disease. Estima-

tions of the plasma chloride were conducted 27 times in 16 patients, 9 of whom had pitting edema of the legs. By the time that edema had appeared most of the patients had received thiouracil in dosages of about one gram daily for intervals of 2 to 5 weeks. Six of the patients with edema had a plasma chloride level between 108 and 116 milli-equivalents per liter.

There was no elevation in the patients without edema. In 2 instances the chlorides were slightly below normal. Estimations of the serum sodium were made 14 times in 12 individuals, 7 of whom had edema. In 5 patients there was from 144 to 150 milli-equivalents of sodium per liter. The serum potassium, estimated in 5 patients, was elevated to 6 milli-equivalents per liter in one. The carbon dioxide combining power of the blood, determined 17 times in 12 patients, ranged from 41 to 48 volumes per cent in 11 instances. The total serum protein was normal in each of 9 patients. The non-protein nitrogen remained normal.

(2) *Androgenic Effects.* The quantity of nitrogen eliminated in the urine decreased during and following treatment in each patient, except for one in whom there was no change (fig. 1). The retention was pronounced in patient M. I. (fig. 2). The amount of creatinine excreted remained constant in one case (fig. 1) but in the other 5 there was a decreased output during and following treatment. These changes were marked in one patient (fig. 3, M. A.). The elimination of creatine remained constant in 4 patients whereas in the other 2 (fig. 2) there was a decrease during and following treatment. Changes in the quantity of 17-ketosteroids excreted in the urine, related to thiouracil treatment, occurred in only one patient (fig. 1, M. E.). This patient had Cushing's disease and was found to excrete 20.6 mg. in 24 hours.

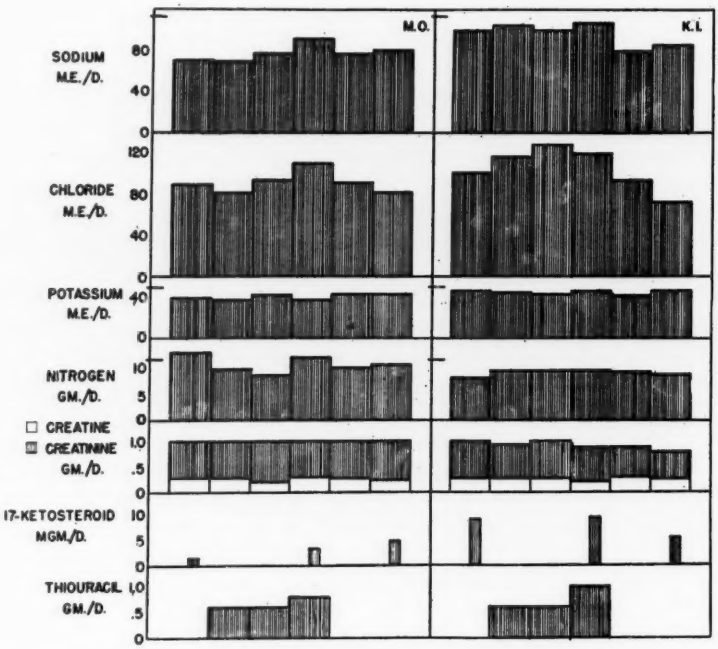

FIG. 1. M. O., a woman aged 55 years, weighing 66 kg., with hyperadrenocorticism, was kept on a constant diet with the following daily intake: carbohydrate, 156 gm.; protein, 72 gm.; fat, 58 gm.; sodium, 114 m.e. (milli-equivalents); and potassium, 50 m.e.

K. I., was also a woman, 45 years old, with hyperadrenocorticism. She weighed 59 kg. and was maintained on exactly the same diet as patient M. O.

Each broad column represents the average amount of the various constituents excreted in the urine daily during an interval of 8 days. The short lines across the abscissae represent the quantity of the substances ingested daily.

During treatment about the same quantity was excreted but 2 weeks after treatment only 7.5 mg. were found. No change in the strength was detected by means of a hand dynamometer. The amount of hirsutism remained about the same, although with more prolonged treatment (6) some slight reduction was noted.

(3) *Gluconeogenesis.* The glucose-insulin tolerance tests, conducted before and after treatment in 5 patients, showed essentially no effect of the thiouracil. The amount of glycosuria was quantified daily in 3 subjects. Two of these patients (M. E. and M. A.) had the adrenal type of diabetes and excreted about 50 grams daily of glucose. The other subject, not discussed in this paper, had a pancreatic type of diabetes and also excreted about 50 grams daily of glucose. Thiouracil was found to have no definite effect on the quantity of sugar excreted.

The basal metabolic rate was estimated at the beginning and at the end of treatment in 4 patients but in no subject was a change noted.

The blood pressure was found to remain at essentially the same level throughout the course of treatment.

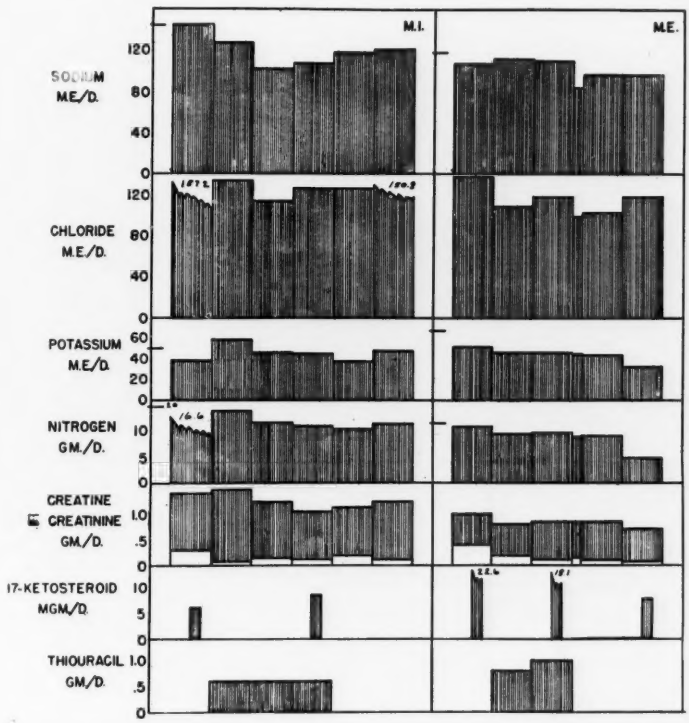

FIG. 2. M. I., a normal man weighing 45 kg., aged 30, was maintained on a constant daily intake of food as follows: carbohydrate, 190 gm.; protein, 131 gm.; fat, 90 gm.; sodium, 145 m.e.; and potassium, 51 m.e. An interval of about 10 days elapsed between the fifth and sixth periods.

M. E., a female patient weighing 68 kg., aged 50, with hyperadrenocorticism (Cushing's type) was maintained on a diet which was almost identical to that of the cases recorded in figure 1: carbohydrate, 150 gm.; protein, 72 gm.; fat, 58 gm.; sodium, 118 m.e.; and potassium, 66 m.e.

Each broad column represents the average daily excretion in the urine for intervals of 8 days.

DISCUSSION

In the interpretation of the effects of thiouracil on certain urinary constituents, one must

bear in mind the possibility that this drug may have a direct action in the kidneys which will promote the excretion of some elements and it may also exert an effect upon one or more endocrine glands causing a decreased excretion

On the other hand it is conceivable that the indirect effect might persist for one or more weeks after discontinuing therapy. If this hypothesis is correct, the quantity of certain elements in the urine would depend upon the

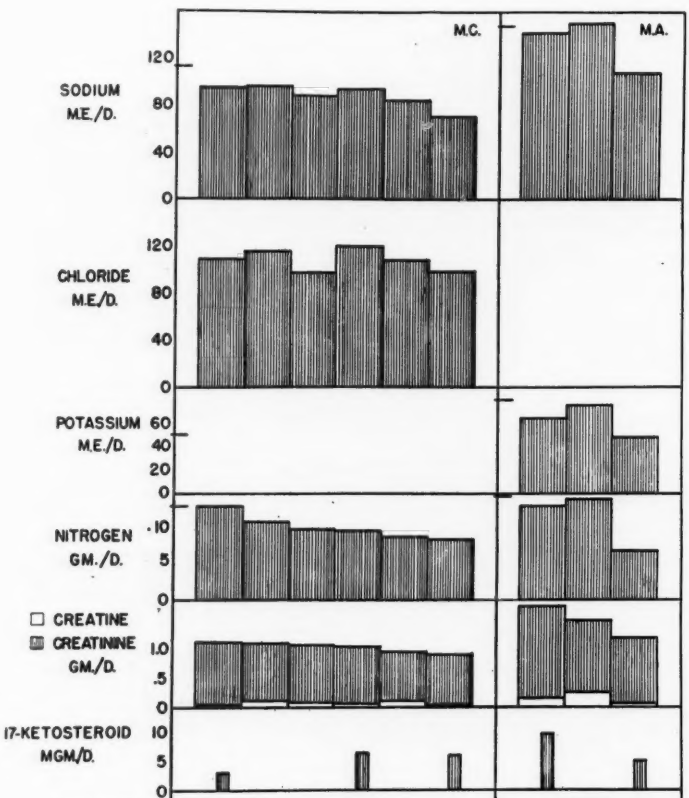

FIG. 3. M. C., a female patient weighing 76 kg., aged 58, with probable hyperadrenocorticism, was maintained on a diet identical to that of the subject in figure 1. This patient had essential hypertension with slight impairment of renal function.

M. A., aged 40, had obesity (weight 121 kg.) and the adrenal type of diabetes. He was kept daily on the following amounts of food: carbohydrate, 162 gm.; protein, 100 gm.; fat, 50 gm.; sodium, 148 m.e.; and potassium, 80 m.e. The decreased excretion of all elements in the last period suggests that the patient failed to save some urine. However, he convinced us that such was not the case.

of certain elements of the body. One would expect the direct effect to exist during the period that thiouracil is being excreted in the urine in appreciable quantities, which begins on the first day of its administration and ends one or two days after discontinuing therapy.

relative activity of the direct and indirect effect, which may vary in different individuals. However, after cessation of treatment only the indirect effect would be expected to exist and the changes in the urine should be more consistent. We have found this to be the case; as

compared with the pre-treatment period, in the post-treatment periods there was in essentially all cases a decrease in the excretion of sodium, chloride, nitrogen and creatinine.

More pronounced alterations could probably be induced by the use of larger doses of thiouracil but this would more likely lead to complications. Furthermore, we had already observed that an occasional thyrotoxic subject receiving the dosage used above developed edema. In these subjects there was no demonstrable cardiac failure, nephritis or hypoproteinemia. In the light of the data which we have presented it is evident that thiouracil caused in certain patients a retention of sodium and chloride, which sometimes was associated with hypernatremia, hyperchloremia, and a decrease in the carbon-dioxide-combining power. However, these changes did not always occur together. These findings suggest the possibility of hyperadrenocortical activity. The decreased excretion of nitrogen, creatinine and creatine could be due to a hyperfunction of the androgenic element of the adrenals. However, there was no well-defined effect on the excretion of the 17-ketosteroids with the exception of one patient. In this case there was a marked decrease in the excretion, which is the opposite from what one might expect. Furthermore, during the same interval, there was no effect on the strength, hirsutism, or blood pressure. The other main activity of the adrenal—gluconeogenesis—did not seem to be affected by thiouracil. None of the changes described can be attributed to a change in the metabolic rate since this was found to remain essentially constant during the period of observation.[5]

Kennedy and Purves (21) found that Brassicae seed, when fed to rats, caused hypertrophy of the adrenal cortex with a great increase in the lipoid content of the cells. Whether the changes induced were due in large part to the thiourea content of these seeds, as is presumably the goiterigenic effect (22), is not known. However, Richter and Clisby (23) found no change in the adrenals of the rats which they treated with phenyl thiourea. Furthermore, we (5) have found in rats that thiouracil had no effect on the weight of the adrenals nor did it produce any histological alterations. Moreover, no histological changes were found in the kidneys, or other organs, excluding the thyroid.

[5] The failure of the basal metabolic rate to decrease during the course of thiouracil treatment, as compared with a marked decline in the basal rate of thyrotoxic patients treated similarly, is probably due to the fact that subjects with normal thyroid function have a much greater amount of thyroxin stored in the thyroid gland and several weeks may elapse before an appreciable depletion of this material results. However, after a month or more of thiouracil administration a distinct fall in the basal metabolic rate results even in normal subjects.

SUMMARY

As part of a series of investigations of the metabolic effects of therapeutic doses of thiouracil, in 16 subjects studies were made of the quantity of various chemical constituents of the blood and urine, the normal amounts of which are known to be influenced, to some extent, by the adrenals. Balance studies were conducted on six subjects, one of whom was normal whereas the other 5 had certain manifestations ascribed to hyperadrenocorticism.

In a few patients, thiouracil in doses of about one gram daily led to a retention of sodium, chloride, nitrogen, creatinine and creatine. Generalized edema occasionally developed and was usually associated with hyperchloremia and hypernatremia, but not with hypoproteinemia or nephritis. Changes in the 17-ketosteroid excretion were not striking, except for a marked reduction following treatment in one patient with Cushing's disease. There were no other alterations in the androgenic functions of the adrenals and none in the gluconeogenetic activities.

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Treatment of Acne Vulgaris

A Preliminary Study on the Value of Pregnant-Mare Serum

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THE MANY opinions which have been advanced concerning the cause of acne vulgaris include bacterial infection, dietary indiscretion, carbohydrate metabolism, ingestion of halogens, local irritation and allergic tendencies. More recently the relationship of the endocrine dyscrasias to acne vulgaris has been studied. There have been many references in the recent literature as to the value of hormones in the treatment of acne vulgaris, but many dermatologists have failed to obtain good results with this form of therapy.

In 1932, Engelbach (1) stated that, "The cytologic alteration occurring in the tissue of the skin and mucous membrane and the hormonic effect on the vasomotor system are responsible for the modification of the sudoriferous and sebaceous excretions." For example, in hypothyroidism, the skin is thick, rough, dry and scaly; whereas in hyperthyroidism it is more apt to be thin, delicate, smooth and velvety. The tendency to early involution and atrophy of these glands producing pre-senile changes is characteristic of hypogonads of either primary or secondary cause. Engelbach further stated that the pituitary sex hormone might be of considerable importance in the treatment of acne vulgaris as well as other dermal changes associated with pituitary types occurring during adolescence.

The occurrence of acne at prepubescence and its frequent disappearance when gonadal function is well established focused the attention of investigators upon the endocrine glands as possible causative factors. Various endocrine medications have been tried and these can roughly be grouped into urinary gonadotropes and estrogens.

Lawrence and Feigenbaum (2) treated 19 girls with acne vulgaris by means of gonadotropic pregnancy urine extracts. Twelve patients were cured, four were improved and three were only slightly aided. In a subsequent report, Lawrence (3) treated 30 patients (10 males and 20 females) with gonadotropic pregnancy urine extracts with excellent results. In six of the female patients, the menstrual period was considered normal, while the others each had some aberration. Many of them presented hypoplasia of the uterus and the breasts. Lawrence considered that most of the female patients were of the hypopituitary, hypogonadal type, because in them were found irregular periods, hypoplasia of the uterus and breasts, flat sugar curves and diminution of estrin.

Lawrence and Werthessen (4) found a significant decrease from the normal in the urinary estrogen excretion by women with acne vulgaris. More important was the change in the androgen-estrogen relationship with an increase in the ratio of androgenic material to estrogenic material measured as estrone equivalents. These findings have clinical confirmation with reports contained in literature discussing the appearance of acne vulgaris in female patients receiving testosterone, and complete cure following the discontinuance of this form of therapy.

Rosenthal and Kurzrok (5) examined the urines of 34 female patients with acne vulgaris who were between the ages of 11 and 54 years. In 27 patients the estrogenic substance was absent. No gonadotropic studies were performed.

Van Studdiford (6) treated 284 acne patients with estrogen and gonadotropic pregnancy urine extracts. Seventy-six of his patients were improved within six weeks.

Hollander and Schmitt (7) noted a beneficial effect in the treatment of acne patients following the ingestion of estrogenic substance. Relapses occurred in 11 of 14 patients upon withdrawal of the medication. The authors felt that the effect of the material was to produce a decrease in the activity of the sebaceous glands.

METHOD

Pregnant-mare serum contains a gonadotropic hormone and is processed by precipitating the hormone from the blood serum of pregnant mares between the sixty-fifth and seventy-fifth day of gestation. The material is greatly refined and is practically protein-free. Because of the possibility that an allergic reaction might be encountered, studies were performed to determine whether any allergens were present. These studies were carried out under the supervision of Dr. Mathew Walzer, Chief of the Department of Allergy at the Brooklyn Jewish Hospital. A number of guinea pigs were injected with normal horse serum while others received injections of pregnant mare serum. A few animals were used as controls. After a sufficient interval, the animals were reinjected with horse serum or pregnant mare serum to test for shock reactions. There were no reactions to horse serum or pregnant mare serum in the guinea pigs previously injected with the pregnant mare serum. Similar experiments were performed, using intestinal and uterine strips. Again, no reactions were noted. From these experiments it was concluded that no allergens were present in the pregnant-mare serum preparation.

When the pregnant-mare serum was first used, it was administered by intramuscular injection. It was our impression that no beneficial effects resulted with this method of administration and therefore intravenous administration was employed. The dosage varied from 400 to 800 international units intravenously, twice a week. To date, more than 5000 injections have been given, without a single reaction.

REPORT OF CASES

The following is the report on a series of 17 female patients with acne vulgaris. All these patients had received the usual treatment including roentgen ray and ultraviolet irradiations, various types of vaccine injections, vitamin therapy, strict dietary limitations and various forms of local medication. Clinical improvement was either slight or only temporary.

Case 1. The value of pregnant mare serum for acne vulgaris was first noted when it was given to a patient who was under treatment for sterility. This patient, L. R., aged 26, complained of sterility of four years duration. Menstruation had begun at the age of 14, occurred every 28 days and lasted for four days. She complained of intermenstrual bleeding. Pelvic findings were entirely normal except for a moderately hypoplastic uterus. Her basal metabolic rate was +4 per cent. A hormonal study, three days premenstrual, revealed no F.S.H. (follicle-stimulating hormone) and five rat units of estrin.[1] An endometrial biopsy, performed immediately before menstruation, revealed only an early secretory phase. She also presented an acne of the face of several years duration. She was given ten injections of 800 international units of pregnant-mare serum intravenously.[2] The intermenstrual bleeding stopped, the acne cleared up completely and she became pregnant. There has been no recurrence of acne.

Case 2. L. S., aged 19, single, had had acne since she was twelve years old. Menses started at 14½ years of age and were always regular. She had considerable x-ray therapy, local medication and vitamin A and D therapy, with no improvement. Physical examination revealed a moderately severe acne of the face and

[1] The F.S.H. was extracted by the alcoholic precipitate method of Zondek as modified by Kurzrok (8). A subcutaneous injection of 0.25 cc. of F.S.H. is given to three immature female mice weighing from 6–8 gms., twice daily for 3 days. The animals are autopsied 100 hours after the first injection. A positive test reveals enlarged reddened ovaries, with large follicles and enlarged and distended uteri, and open vagina. A negative test shows small white ovaries and a threadlike uterus.

Estrone was extracted by the Berger and Smelzer modification of the Kurzrok and Ratner method, after preliminary hydrolysis of the urine with concentrated hydrochloric acid. The estrone in varying doses is then injected into 3 castrated rats weighing roughly 200 gms. The smallest amount which gives a positive cornified smear is then called a rat unit.

These tests are comparatively accurate for the amount of hormone usually found in the average adult female.

[2] We wish to thank the Schering Corporation for their generous supply of pregnant mare serum (Anteron) and estradiol benzoate (Progynon-B).

shoulders associated with a moderate, generalized hirsutism. The thyroid was slightly enlarged; the breasts were small and the uterus and cervix were hypoplastic. Her basal metabolic rate was −12 per cent. Serial vaginal smears ranged from three plus to three minus. Serial pH studies ranged from four to five. A hormonal study revealed no F.S.H. and negative estrin. She was given one-half grain of thyroid, three times a day for three months. There was no improvement of the acne. She was then given 43 injections of 400 international units of pregnant mare serum intravenously. The acne improved considerably following this treatment. At this time, she was given 2000 R.U. of estradiol benzoate for six weeks in an effort to increase the size of the uterus and the cervix. The acne flared up again and the estrogen was discontinued. She then received another course of pregnant-mare serum injections, for two months. Following this, the eruption underwent involution. When she was examined seven months later there had been no exacerbation. A hormonal study at this time revealed no F.S.H. and 8 R.U. of estrin.

Case 3. R. K., aged 21, single, had acne since she was 15 years old. Menses had started at 15 and were always irregular. She had periods of amenorrhea for two and three months at a time, but no dysmenorrhea or breast complaints. Physical examination revealed moderate acne vulgaris of the face and slight hirsutism of the upper lip, breasts and legs. The uterus was almost normal in size but the cervix was hypoplastic. Her weight was 163 pounds. Her basal metabolic rate was −14 per cent. A hormonal study revealed no F.S.H. and a negative estrin. She was given a one-thousand-calorie diet and one-half grain of thyroid a day. She lost weight but the acne persisted after she had followed this regime for four months. She was then given 800 international units of pregnant-mare serum, intravenously, twice a week for ten weeks. The acne cleared up and the menstrual periods became regular. A hormonal study three years later revealed no F.S.H. and 15 R.U. of estrin.

Case 4. M. H., aged 22, married, had acne of the face and back of several years duration. She also complained of obesity, irregular menstruation with prolonged periods of amenorrhea and sterility of three years' duration. She weighed 171 pounds. Her breasts were pendulous. Vaginal examination revealed a deep vagina, deep symphysis and hypoplasia of the uterus and cervix. Her basal metabolic rate was −12 per cent. A hormone study revealed no F.S.H. and a negative estrin. She was given a one-thousand-calorie diet which was low in fat and carbohydrate and one-half grain of thyroid per day. She followed this regime for two months, during which time she lost 25 pounds without any improvement of the acne or menstrual irregularities. She was then given 10,000 R.U. of estradiol benzoate, twice a week for two months, and the uterus and cervix became practically normal in size but the acne became worse. She then received 800 international units of pregnant-mare serum, intravenously, twice a week for three months. The acne cleared up completely and she menstruated about every five weeks. (A hormonal study two years later revealed no F.S.H. and a negative estrin.) There has been no recurrence of acne but she has not become pregnant and her periods occur every five to six weeks.

Case 5. P. N., aged 17, single, had acne of six months' duration. Six months after an operation for appendicitis, one year ago, she first developed ovulation pain. Menses started at 12 years of age, were irregular (5 to 15 days late) and were accompanied with menorrhagia but no dysmenorrhea. Physical examination revealed a slightly enlarged thyroid. Her breasts were normal in size. There was mild facial acne but no hirsutism. Rectal examination revealed the uterus and cervix to be slightly smaller than normal. The right ovary was tender and adherent to a right lower quadrant scar. Her basal metabolic rate was −7 per cent. A hormonal study revealed no F.S.H. and traces of estrin. She received 15 injections of 400 international units of pregnant-mare serum intravenously and the acne and ovulation pain disappeared. A hormonal study six months later revealed no F.S.H. and 10 R.U. of estrin.

Case 6. E. L., aged 27, single, had cystic acne of several years' duration. Menses had started at 13 years of age and occurred every 28 days, lasting four days. She had received x-ray therapy and local treatment for the acne with only temporary improvement. Physical examination revealed a moderate cystic acne and hirsutism of the face. The thyroid was palpable. Vaginal examination revealed endocervicitis and slight hypoplasia of the uterus and cervix. The basal metabolic rate was +3 per cent. Serial vaginal smears were all three minus and serial pH studies ranged from five to six. A hormonal study revealed negative F.S.H. and a negative estrin. She was given 16 injections of 400 international units of pregnant-mare serum intravenously and the acne cleared up completely. A hormonal study four months later revealed no F.S.H. and 12 R.U. of estrin. There has been no recurrence of the acne.

Case 7. R. K., aged 32, married, had acne for several months, which was becoming progressively worse. She had two children. Her periods were irregular, being delayed from three to 18 days. Physical examination revealed a moderate facial acne, most severe around the chin. The uterus and cervix were normal in size. A hormonal study revealed no F.S.H. and a negative estrin. She received 28 injections of 400 international units of pregnant-mare serum intravenously. Her periods became normal and regular. The acne eruption underwent involution. A hormonal study since that time revealed no F.S.H. and 8 R.U. of estrin.

Case 8. E. R., aged 27, single, had severe cystic acne of many years' duration. There was a decided exacerbation of the acne a few days before the onset of each

menstrual period. There was only temporary improvement following x-ray therapy and local treatment. Her menses were always regular and scant. Physical examination revealed a severe cystic acne of the face. The thyroid was slightly enlarged. The breasts were underdeveloped and the uterus and cervix were hypoplastic. Serial vaginal smears ranged from three to four with serial pH studies ranging from four to eight, mostly six. A roentgenogram of the sella turcica was normal. A hormonal study revealed no F.S.H. and no estrin. Her basal metabolic rate on two occasions was +40 per cent and +33 per cent. She received 33 injections of 800 international units of pregnant-mare serum intravenously, the last one in February, 1941. Her skin cleared up completely and remained clear until October, 1941, when she developed a slight exacerbation of the acne. She then received eight additional injections of pregnant-mare serum and there has been no recurrence of the acne since. A hormonal study a few months later revealed no F.S.H. and 20 R.U. of estrin.

Case 9. O. S., aged 30, married, had a moderate acne of several years' duration. Her chief complaint, however, was sterility. Menses had started at the age of twelve, occurring every 28 days and lasting four days. Her periods disappeared at the age of 14 years for one year. They then became irregular until she was 22 years of age, at which time she had a seven-month-old stillbirth. She had not menstruated for seven years. Physical examination revealed dry skin with a moderate seborrhea of the scalp, moderate acne of chin and cheeks, but no hirsutism. The uterus and cervix were slightly hypoplastic. A hormonal study revealed no F.S.H. and traces of estrin. An endometrial biopsy revealed a resting endometrium. She received 31 injections of 400 international units of pregnant-mare serum intravenously. After three months of therapy the acne cleared and the patient began to menstruate. The amenorrhea recurred after therapy was discontinued but there was no exacerbation of the acne. For the past 18 months she has received intermittent treatment with estradiol benzoate for the hypoplasia of the uterus and cervix. During this time, however, she developed an exacerbation of acne. The patient began to menstruate again and the acne has cleared up since the estrogen was discontinued. She has not, however, become pregnant. Several hormonal studies since have revealed no F.S.H. and no estrin.

Case 10. S. C., aged 17, single, has had acne since the onset of menstruation at the age of 12. The menses occurred every 21 days and lasted four days. For the past few months she menstruated every two to three weeks. There were no molimina. Her basal metabolic rate was +3 per cent. A hormonal study revealed no F.S.H. and no estrin. Physical examination revealed a moderate acne of the face and back. The thyroid gland appeared normal. She received eight injections of 400 international units of pregnant-mare serum intravenously, during which time the acne improved considerably but she failed to continue treatment. No further hormone studies were obtained.

Case 11. B. B., aged 16, single, had a moderate acne of the face and back associated with slight hirsutism of the upper lip and the chin. She also complained of irregular menses since the onset at the age of 13. Physical examination revealed her to be a tall, hypogonadal type. On rectal examination she presented a moderate hypoplasia of the uterus and the cervix. Her basal metabolic rate was −17 per cent. A hormonal study revealed no F.S.H. and 3 R.U. of estrin. Serial vaginal smears ranged from three to four, with serial pH studies ranging from four to five. She received one-half grain of thyroid daily, for three months. There was no improvement in either the menstrual condition or the acne. She then received 12 injections of 400 international units of pregnant-mare serum intravenously. Her periods became regular and the eruption cleared completely. There has been no exacerbation of the acne for the past 18 months. A hormonal study since, has revealed no F.S.H. and 16 R.U. of estrin.

Case 12. H. R., aged 25, single, had a moderate acne of the face and back, associated with slight hirsutism of the upper lip, face and extremities of several years duration. She also complained of pain in the right lower abdominal quadrant occurring periodically between periods since she was 17 years old. Menses started at the age of 17, were irregular, occurring once or twice a year for one day and accompanied with severe headaches and painful breasts one day premenstrually. Physical examination revealed the thyroid to be slightly enlarged, with a nodule the size of a prune in the right lobe. The breasts were underdeveloped. There was slight tenderness in the right lower abdominal quadrant. The uterus was hypoplastic and levorotated. The left ovary was slightly cystic and tender. Her basal metabolic rate was −4 per cent. Serial vaginal smears ranged from three to three minus with serial pH studies ranging from six to eight. A roentgenogram of the sella turcica was normal. A hormonal study revealed no F.S.H. and no estrin. She received 400 international units of pregnant-mare serum twice a week for two months. The acne cleared up and her menses became normal. There has been no recurrence of the acne for the past 20 months. A hormonal study six months after treatment was discontinued revealed no F.S.H. and 6 R.U. of estrin.

Case 13. C. G., aged 31, married, had a severe cystic acne which began nine years ago, following the birth of a child. Her menses had started at the age of 13, occurring every 30 days and lasting for five days. There was no dysmenorrhea or headaches but slight premenstrual breast discomfort. The acne was worse one week before menstruation. Physical examination revealed severe acne of the face, chest and back and moderate seborrhea of the scalp. The breasts were normal. Vaginal examination revealed the uterus to be retroverted, normal in size and to contain a small fibroid, posteriorly. There was also a moderate vaginitis. Serial vaginal smears ranged from three to four, with serial pH studies ranging from four to seven. A hormonal study revealed F.S.H. and 7 R.U. of estrin.

A premenstrual endometrial biopsy revealed a late secretory endometrium. Her basal metabolic rate was −12 per cent. She was given one-quarter grain of thyroid twice a day with no improvement. This patient was treated with pregnant-mare serum although her endocrine findings were apparently normal. She received 30 injections of pregnant-mare serum intravenously and the acne was improved considerably while she was receiving therapy. There was, however, a recurrence when the treatment was discontinued. There was a prompt improvement when these injections were resumed, followed by another slight exacerbation when they were discontinued for the second time. Hormonal studies have not been repeated.

Case 14. R. S., aged 14, single, developed acne vulgaris six months after the onset of her menses, which began at the age of ten and one-half years. The periods occurred every 28 days and there were no molimina. Physical examination revealed a severe facial acne and a moderate acne of the chest and back. There was no hirsutism. She was five feet six inches tall and weighed 111 pounds. Her blood pressure was 90/50 and her hemoglobin was 55 per cent. Her breasts were normal. Rectal examination revealed a hypoplastic uterus and cervix. Her basal metabolic rate was −23 per cent. Serial vaginal smears ranged from three to four with serial pH studies ranging from five to eight. A hormonal study revealed no F.S.H. and no estrin. She was given one grain of thyroid three times a day for a period of three months. There was no improvement of the acne. Then she was given 20 injections of 400 international units of pregnant-mare serum intravenously and the acne improved greatly. She failed to continue therapy and has not been seen since. Hormonal studies have not been repeated.

Case 15. J. M., aged 22, single, had a severe cystic acne of several years duration, which became worse at each menstrual period. The menses had started at the age of 13, occurred every 28 days and lasted four days with slight dysmenorrhea and premenstrual breast pains. Physical examination revealed a fairly obese patient. The thyroid and uterus were normal in size. There was a severe cystic acne of the face, back and chest. Her basal metabolic rate was zero. Hormonal studies revealed no F.S.H. and no estrin. The sugar tolerance was normal and the blood cholesterol was 246 mg. per cent. Serial vaginal smears ranged from plus two to minus three with serial pH studies ranging from five to seven. She received 13 injections of 800 international units of pregnant-mare serum intravenously over a period of six weeks without any improvement, at which time she discontinued treatment.

Case 16. R. K., aged 16, single, had a severe acne of the face, seborrhea of the scalp, small breasts and severe hypoplasia of the uterus and cervix. There was also a mild hirsutism of the face and legs. Her basal metabolic rate was +4 per cent. Serial vaginal smears ranged from plus two to minus three with serial pH studies ranging from four to eight. Hormonal studies revealed no F.S.H. and 7 R.U. of estrin. The blood sugar tolerance revealed a tendency towards a diabetic status. She was given 400 international units of pregnant-mare serum intravenously twice a week and the acne began to improve after three months of therapy. At this time the pregnant-mare serum was discontinued and she was given 0.5 mg. of oral estrogen in an effort to stimulate growth of the uterus, cervix and breasts. While she was taking the estrogen, there was a severe exacerbation of the acne so that this medication had to be discontinued. She was then given 800 international units of pregnant-mare serum intravenously and the acne practically disappeared. A hormonal study at this time revealed no F.S.H. and 7 R.U. of estrin.

Case 17. A. L., aged 19, single, had acne of many years' duration. The menstrual periods were scanty but regular. She had had considerable x-ray therapy and local treatment without improvement. There was a moderate hypoplasia of the cervix. Her basal metabolic rate was −13 per cent. A hormonal study revealed no F.S.H. and no estrin. Serial vaginal smears ranged from two to three with serial pH studies ranging from four to five. She had been taking one-quarter grain thyroid daily for several months without any improvement of the acne. She received some estrogen and the acne was made worse. She then received 47 injections of 400 international units of pregnant-mare serum, intravenously. The acne completely disappeared and her periods became regular. She has had no recurrence of the acne since her treatment was discontinued 16 months ago. A hormonal study since then revealed no F.S.H. and 8 R.U. of estrin.

COMMENT

It is not the intention to infer that pregnant-mare serum is a cure for acne vulgaris. Investigation has shown that certain cases respond to different types of endocrine therapy. The suggestion is made that any case of acne in the female, which is influenced by the menstrual cycle, should have a thorough endocrine study to determine if possible the primary difficulty and the condition should be treated accordingly.

SUMMARY

The cases are reported of 17 patients, suffering from acne, who had some associated menstrual disturbance. Most of them presented evidence of some degree of hypopituitarism. Hormonal studies revealed negative follicle-stimulating hormone and negative estrin in 12 of 17 of the cases. Subsequent hormonal studies revealed no change in two patients and normal

findings in ten patients. Five patients failed to return for a recheck. Fourteen of the 17 patients were definitely improved by injections of pregnant-mare serum. The administration of estrogen alone aggravated the eruption of acne. Six of the 17 patients had some degree of hirsutism which was not altered by treatment with pregnant mare serum.

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Hyperinsulinism as an Etiologic Factor in Acute Rheumatic Fever

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INTRODUCTION

THAT DIABETICS are largely free of allergic diseases is well known (1) whereas allergic individuals are prone to hyperinsulinism (2, 3). Diabetics have far less than their expected quota of peptic ulcers (4) and experimental evidence supports the view that these lesions, too, are accompanied by hypoglycemia that suggests hyperinsulinism. Another disorder seldom seen in diabetics is rheumatic fever (Joslin, 5). This disorder, according to Levine (6), represents an allergic reaction to the products of the causative organisms. Levine's conclusion is supported by the fact that bacteria have not been isolated from accessible rheumatic lesions.

The appearance of allergic symptoms requires, in addition to contact with the *specific* allergen—in the case of rheumatic fever, bacteria or their toxins—the presence of a *non-specific* constitutional factor. In other types of allergy, it has been shown that this constitutional factor is, in some way, connected with hyperinsulinism since that metabolic abnormality was found in all the cases of allergy that were investigated (2, 3). Furthermore, functional hyperinsulinism (as distinguished from cases of islet-cell neoplasm) can be eliminated by dietary treatment and the glucose-tolerance test will give experimental verification in each case (7). Such purely dietary treatment has been administered to allergic individuals with amelioration of their symptoms and without recourse to any specific treatment at all (2, 3). In other words, correction of the non-specific factor alone was sufficient to prevent the appearance of allergic symptoms in spite of the continued presence of the offending allergen. Since rheumatic fever is allergic in nature, we should expect, by analogy, to find it associated with hyperinsulinism. This would account for the diabetic's immunity to it.

OBSERVATIONS

In an investigation of the suggested relationship, the six-hour glucose tolerance test of Harris (8) was performed on several patients who had recovered from recent attacks of rheu-

TABLE 1. BLOOD SUGAR TEST RESULTS

Case	Age Yrs.	Wt. Lbs.	Attack[1]	Dosage Gm.	Blood Sugar mg./% at 1-Hour Intervals						
					0[2]	1	2	3	4	5	6
1	14	84	3rd	70	75	138	82	72	74	66	58
2	12	73	3rd	65	88	148	104	86	71	63	61
3	10	63	1st	50	82	128	80	76	66	59	
4	16	102	2nd	80	80	144	102	88	64	64	61
5	18	136	3rd	100	92	150	98	76	62	54	50
6	13	79	2nd	70	78	142	92	76	64	60	65

Mg. glucose per 100 cc. of blood (capillary) (by micro Folin-Wu method).
[1] No. of current attack in patient's rheumatic history.
[2] Fasting level.

matic fever during the winter of 1939–40. In each case the temperature and sedimentation rate had become normal. The results shown in table 1 were secured. The final blood-glucose values were all well within the hypoglycemic range.

The patients were then placed on the Harris diet (7). This consists of frequent feedings with a high fat and low, quickly-absorbable carbohydrate diet; sweets and other rich carbohydrate foods and caffeine beverages are forbidden. The patients were instructed to follow the diet closely for three months. Then they were permitted gradually to drop the extra feedings. By the end of six months they were on the usual three-meals-a-day schedule. However, they continued to avoid caffeine and sweets and they kept the consumption of potatoes and other carbohydrate-rich foods to a minimum.

TABLE 2. BLOOD SUGAR TEST RESULTS AFTER DIETING

Case	Blood Sugar Mg./% at 1-Hour Intervals						
	0[1]	1	2	3	4	5	6
1	78	144	82	84	80	80	78
2	84	136	90	86	84	76	80
3	98	138	104	90	88	92	90
4	102	142	110	102	94	88	78
5	86	138	92	84	86	82	80
6	80	142	94	82	78	82	84

Mg. glucose per 100 cc. of blood (capillary) (by Folin-Wu micro-method).
[1] Fasting level.

After these six months the patients were tested again. The results are indicated in table 2. It is seen that the Harris diet had the anticipated effect of eliminating the hyperinsulinism. All of these patients then went through two winters without any further rheumatic attacks whatever.

During the winter of 1940–41 another group of patients were managed in the same way. The results of the initial glucose-tolerance curves are set forth in table 3. In all cases evidence of hyperinsulinism was disclosed. These patients were also given the Harris diet. However, it was not possible to test them again because of interruption due to the war. Three of these patients had had many attacks of rheumatic fever. The entire group went through the following winter without a single attack of rheumatic fever.

It was deemed advisable to see whether "inactive" rheumatics also have hyperinsulinism. During the summers of 1940 and 1941, when the danger of an exacerbation would probably be minimal, several inactive cases with definite histories of previous attacks and evidence thereof in the form of valvular defects were tested with a simplified glucose tolerance test (9). This consisted of furnishing the patient with a quantity of glucose solution suitable to his body weight with instructions to eat nothing else after his evening meal. He arose at 4 A.M., drank the solution and went back to sleep. A single blood-glucose determination was made at 10 A.M., after which he was permitted to break his fast. Under these conditions, a blood-glucose concentration below 70 mg. per 100 cc. (capillary blood) indicates hyperinsulinism. These patients had been carefully selected to weed out any with known histories of other allergic disorders since it had already been demonstrated that ordinary allergics would respond positively to this test (2).

It was found that these patients could be divided into two groups:

I. 78, 82, 72, 71 and 88 mg. glucose per 100 cc. of blood.

TABLE 3. BLOOD SUGAR TEST RESULTS

Case	Age Yrs.	Wt. Lbs.	Attack[1]	Dosage Gm.	Blood Sugar Mg./% at 1-Hour Intervals						
					0[2]	1	2	3	4	5	6
7	46	163	?	100	70	143	108	80	67	58	56
8	13	75	3	65	76	135	94	92	74	68	62
9	28	145	?	100	82	142	96	82	72	66	60
10	42	128	?	100	80	138	100	80	82	74	66
11	14	82	3	70	92	146	96	86	72	61	65

Mg. glucose per 100 cc. of blood (capillary) (by micro Folin-Wu method).
[1] No. of current attack in patient's rheumatic history. "?" = many attacks.
[2] Fasting level.

II. 64, 62, 62, 48, 58, 64, 70, 65, 66, 60, 62 and 64 mg. per 100 cc.

These patients were all advised to follow the Harris diet for several months and then to return to the more usual three meals a day but to continue the avoidance of caffeine beverages and sweets. It was possible to repeat this test with the first five patients in group II after they had followed the diet for six months. These patients had been especially chosen because they had had repeated exacerbations of rheumatic fever. The new blood glucose values were 82, 86, 76, 90 and 88 mg. per 100 cc. These values are normal. The first three of these patients had very severe sore throats during the following winter but in no case did the feared rheumatic exacerbation materialize. Of the entire two groups, no patient had any rheumatic attack for two winters.

DISCUSSION

In the previous work with allergics, it was shown that such persons, whether suffering from protein or bacterial allergy, had hyperinsulinism (2). When the metabolic abnormality was corrected by appropriate dietary measures, the purely allergic manifestations disappeared. In particular, the cases of perennial asthma due to chronic bronchitis no longer had any asthmatic attacks or, at least, had only minimal discomfort although the underlying infection in the bronchial tree was entirely unaffected. Thus, in spite of the continued presence of the allergen (the bacteria lodged within the respiratory apparatus), the patients had lost the allergic response with the elimination of their hyperinsulinism. They then became persons with chronic bronchitis but without asthma.

The results obtained above with the active rheumatics followed the same pattern. They all had hyperinsulinism and, with the correction of that metabolic disorder, they no longer had their accustomed allergic reaction (a rheumatic exacerbation) to further respiratory infections presumably of the same nature as those which had been followed by such exacerbations in the past.

Patient No. 7 is of peculiar interest. She had double mitral and aortic disease and had been fibrillating for a number of years. She maintained a fair degree of compensation with digitalis and only moderate curtailment of activity. During the summer of 1939, she had symptoms of bronchial asthma for the first time. This was found to be due to ragweed. Because of the interest in asthma, she was urged to submit to a glucose-tolerance test but she refused. She did not wish to follow any diet but she did agree to eliminate caffeine and sweets. She passed through the hay fever season with the aid of an occasional capsule of ephedrine and amytal. During the early spring of 1940, she had her most recent exacerbation of rheumatic fever. She then consented to have a glucose-tolerance test, the results of which are given above. Then she followed the diet religiously. During the next summer (1940), she had no asthmatic symptoms at all although she had in the meantime moved into a house with a patch of ragweed only a few feet away. She had a particularly bad sore throat the following winter but no rheumatic sequelae developed. During the next summer, too, she was free from asthmatic symptoms. She sustained a cerebral embolus in the autumn and died after a few days. She was the only patient in the entire group investigated with any protein allergy in addition to rheumatism.

The "inactive" cases fell into two groups. Most of them gave positive evidence of hyperinsulinism. A smaller number did not. Each of these latter cases had had but one attack of rheumatic fever and that many years ago. Careful questioning brought out the interesting fact that these patients were not coffee drinkers and they did not care particularly for sweets.

The larger group of "inactive" cases did give evidence of hyperinsulinism. Those whom it was possible to follow up had the regular response to the Harris diet in that the hyperinsulinism was no longer present. These patients then had sore throats without any rheumatic sequelae, acting in this manner just like the "active" cases. All but two of these patients had had several exacerbations and these two patients had fairly high blood glucose levels—66 and 70 mg. per 100 cc., respectively. All of these patients demonstrated the effectiveness of the diet in preventing further exacerbations.

The findings above recorded have received indirect confirmation. Coburn and Moore have demonstrated a relation between the acquisition of rheumatic fever following sore throats and previous feeding habits (10). They found that all of their rheumatic patients had been eating insufficient amounts of protein. An ex-

haustive analysis of the diets showed that all other dietary factors, including minerals and vitamins, were adequate. The protein intake was increased and, although the incidence of sore throats was unchanged, there was a practically complete elimination of rheumatic sequelae. It is reasonable to assume that any previously existing hyperinsulinism was eliminated by the change in diet. Unfortunately glucose-tolerance tests were not reported.

The diet of the poor is apt to contain disproportionate amounts of the cheaper carbohydrate foods such as bread and, especially, potatoes. The preponderant incidence of rheumatic fever among the inhabitants of the slums is well known. Warner, Winterton and Clark have noticed and commented upon this dietary unbalance among rheumatics (11). They increased the milk and butter allowances of the children under their care and they obtained a marked drop in the incidence of rheumatic attacks though there was no significant change in the number of sore throats. However, there was a reduction to one-third of the former incidence of rheumatic attacks. In the cases of Warner, Winterton and Clark and of Coburn and Moore, the one common characteristic in the two otherwise different procedures—on the one hand, increase in protein, and on the other, increase in fat—is the recognized alleviating effect that they have on hyperinsulinism.

It is regretted that ill health precludes further work by the author on this problem. The results of the incomplete study are reported in the hope that others will be moved to extend the investigation.

SUMMARY

Attention is called to the fact that diabetes (hypoinsulinism) and rheumatic fever seldom co-exist. Evidence is cited that allergic disorders are characterized by hyperinsulinism. Since rheumatic fever is a variety of bacterial allergy, it was postulated that rheumatic subjects should also have hyperinsulinism. Glucose tolerance tests in 11 patients having rheumatic fever disclosed that such was the case. Dietary treatment of the endocrine abnormality with resultant normalizing of the blood-sugar curves resulted in freedom from further rheumatic attacks.

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Role of the Endocrines in the Regulation of Blood Sugar[1]

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DESPITE THE fact that food-intake in the human is an intermittent affair, occurring at arbitrarily fixed intervals without any known relation to natural laws, the blood sugar is usually maintained at a constant level. It is therefore obvious that man possesses blood sugar regulating mechanisms of a high order of efficiency. Otherwise there would be too much sugar present in the blood at three periods of the day, and too little at all other times. Hyperglycemia does not represent nearly so immediate a threat to the well-being of the body as does hypoglycemia. It is not surprising, therefore, that nature has provided a multiplicity of factors which regulate the blood sugar level and that most of these are directed towards the avoidance of hypoglycemia. Of these blood sugar regulators the endocrine glands form an important part.

Glucose (dextrose) constitutes the only important form of blood sugar and, in the post-absorptive state, originates in the liver and in the liver alone. It is the function of the liver to supply sugar to the blood and, through it, to the other tissues of the body when sugar is not forthcoming from the gastro-intestinal tract. Experimental removal of the liver in a large variety of animals has shown that this procedure is invariably followed by the rapid development of profound hypoglycemia within about two hours (1). This is true whether the animal is young or old, fed or fasted, intact or lacking various and sundry organs or endocrine glands. It is thus apparent that the extra-hepatic tissues continuously and under all circumstances utilize the blood sugar at a relatively rapid rate. Since in the intact animal under these same circumstances the blood sugar level is maintained, it is equally apparent that in the post-absorptive state the liver can and does continuously supply sugar to the blood. The remarkable constancy of the blood sugar level therefore represents a finely maintained balance between the utilization of sugar on the one hand and its production by the liver on the other.

Submitted by request.

[1] Presented before the Session on Endocrinology, American College of Physicians, Chicago, Illinois, on October 11, 1943.

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THE HOMEOSTATIC MECHANISM OF THE LIVER

The much used (and often sadly misinterpreted) dextrose tolerance test is in fact merely an artificial strain put upon the regulating mechanism in a quantitative form and in a manner duplicable at will under the same conditions. The so-called normal dextrose tolerance curve is an index of the high regulative efficiency which is ordinarily found. Even when amounts of sugar which are much larger than those ordinarily encountered in feeding are administered orally, the disturbance in the blood sugar level is overcome within about two hours.

Until a few years ago it was customary to explain the normal dextrose tolerance curve as resulting from a stimulation of the pancreas by the administered sugar. The consequent secretion of insulin was supposed to dispose of the incoming sugar by increasing the rates of storage and oxidation of carbohydrates. The abnormal type of curve characteristic of the depancreatized animal and the diabetic human was attributed to a lack of pancreatic response, with a consequent inability to dispose of the incoming sugar at the normal rate. It will be noted that this explanation ignored the important rôle of the liver in supplying sugar and the possibility that regulation might

also be accomplished by controlling this supply.

It occurred to myself and coworkers (2) that it was possible to test these conceptions in a relatively simple manner and we argued as follows: if we take a completely depancreatized dog and inject insulin intravenously from a constant injection pump at a rate just sufficient to maintain a normal, constant blood sugar level, we will have restored that dog to normal in a restricted experimental sense. He will, however, differ from a really normal animal in that, when a dextrose tolerance test is performed, he will not be able to mobilize additional insulin, but will have to get along on the constant amounts of insulin which he is receiving from his artificial substitute for a pancreas. If the previous concepts are correct, such an animal should yield "diabetic" tolerance curves. Actual performance of the experiments revealed that under those conditions the animals yielded perfectly normal dextrose tolerance curves! It was evident that, *providing sufficient insulin were present to maintain a constant blood sugar level*, no additional secretion of insulin was necessary in order to obtain a normal dextrose tolerance curve.

The above results naturally directed our attention towards the liver as the factor which did vary in regulation. We hepatectomized normal dogs leaving the pancreas intact, and substituted a constant injection of dextrose just sufficient to maintain a normal constant blood sugar level. In other words this type of animal preparation was able to mobilize insulin as required, but it could not alter the rate at which sugar was delivered to its blood from the artificial liver. Such animals invariably yielded markedly "diabetic" tolerance curves. It was clear that it was the liver rather than the pancreas that was essential to the regulating mechanism which resulted in the normal dextrose tolerance curve. Further investigation indicated that, when the blood sugar is raised by the administration of sugar, the liver responds to this stimulus by decreasing the amount of sugar which it was formerly supplying to the blood from its own resources.

This homeostatic regulating mechanism for the control of the blood sugar level was later subjected to direct proof (3). By correlating the rate of blood flow through the liver of experimental animals with the difference in the sugar content between the blood flowing into and out of this organ, it was possible to calculate the absolute amounts of sugar entering and leaving the liver, per unit of time. Figure 1 illustrates such an experiment and shows what happens when a dextrose tolerance test is made. It may be seen that the liver, which was putting out sugar into the blood prior to the administration of the dextrose, ceased to do so almost immediately and started to take in large quantities of sugar. The period following this retention of sugar is particularly worthy of note. At this time the liver neither takes in nor puts out sugar for a period of about an hour, showing that the inhibition of the output of sugar is a separate phenomenon from the storage of sugar. When the period of inhibition was over, the liver again began its usual supply of sugar to the blood and the blood sugar level which had fallen somewhat below the pre-test level during the inhibition rose to slightly above its pre-test level.

The hepatic regulating mechanism is analogous to the system used for regulation of temperature in many modern homes, namely, the thermostat-furnace arrangement. When the temperature of the house rises above the level at which the thermostat has been set, the furnace shuts off until the excess heat has been dissipated. When the temperature of the house falls back to the threshold of the thermostat, the furnace starts up again. That is exactly what the liver does so far as the blood sugar level is concerned. It will be noted that just as it is the room temperature which operates the thermostat and shuts off the furnace, so it is the blood sugar level that inhibits the output of sugar by the liver.

The above analogy is useful in arriving at a clear conception of the function of the endocrine glands in the regulation of the blood sugar. A thermostat-furnace arrangement will go through the same regulating processes at any temperature level; it is the setting of the thermostat which determines at what temperature the furnace will shut off. The balanced action of the endocrine secretions determines the level of blood sugar at which the liver will be inhibited. In the normal animal the endocrine balance is such that the liver is

inhibited at a range between 80–100 mgm. per cent. This indeed is what determines the existence of a constant normal blood sugar level. An excess or a deficiency of any of the hormones upsets the endocrine balance and changes the threshold for the inhibition of the liver, and hence changes the blood sugar level accordingly.

INFLUENCE OF THE PANCREAS

It will be remembered that while the liver was stated to be the primary organ in which the regulating-activity responsible for the dextrose tolerance curve resided, it was necessary to maintain a constant supply of insulin throughout the test period. In other words, the normal endocrine balance had to be maintained in order to have regulation occur at its usual normal level. When insulin is deficient, as in experimental pancreatic diabetes, the situation is equivalent to that which would occur if the adjusting screw on a thermostat were set at an infinitely high level. If we suppose that the setting were now at 1,000°F., the thermostat might just as well have been entirely removed for all practical purposes. In the first place the furnace is probably incapable of producing enough heat to raise the temperature of the house to 1,000°F. and so to shut itself off. Secondly, even if the furnace were capable of producing that much heat, the house would burn down before the thermostat threshold was reached. What actually happens is that the furnace simply continues to produce heat in an uncontrolled manner to the limit of its capabilities. The house is overheated and the heat is dissipated only to the extent that it can pass through the walls, doors and windows. Similarly, when insulin is deficient the sugar output of the liver is no longer inhibited regardless of how high the blood sugar level rises. The result is a hyperglycemia and glycosuria which are only aggravated by the administration of additional sugar. When the latter procedure is performed as a dextrose tolerance test, the result is a high and prolonged curve which is not a function of the normal liver reaction, but which depends upon the rate at which the sugar can be disposed of by diffusion, utilization and excretion.

It is understood, of course, that the latter processes also play some part, though a minor one, in the regulation of the blood sugar of normal animals. For example, there is evidence

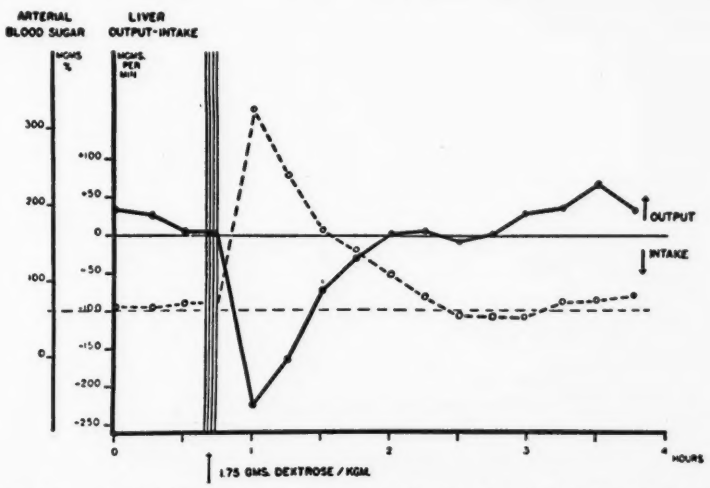

FIG. 1. The effect of dextrose administration upon the output and intake of sugar by the liver of an intact dog, calculated from blood sugar values and thermostromuhr measurements of hepatic bloodflow (3). The broken line represents arterial blood sugar values; the heavier continuous line represents output or intake of sugar by the liver in mgm. per minute. Note the immediate cessation of sugar output when sugar is administered and the large intake of sugar which follows. Throughout the second hour after sugar administration the liver neither retains nor excretes sugar. During this period the level of sugar in the arterial blood falls below its original control values and does not return to normal until after the liver has resumed its output. The inhibition of the hepatic secretion of sugar is, therefore, a real and separate phenomenon from the storage of sugar.

that both in the presence and in the complete absence of insulin the rate of utilization of sugar depends upon the height of the blood sugar level (4). Hence the sharp rise in the blood sugar consequent to sugar administration does cause the utilization of some additional sugar. There is, furthermore, the factor of the storage of sugar as glycogen in all tissues, but especially in liver and muscle. The rate of this storage is also dependent upon the concentration of sugar in the blood and is therefore increased after sugar administration (5). All these subsidiary mechanisms, however, can not compensate, so far as regulation is concerned, for the active participation of the liver in the process. This was clearly shown by the experiments on the hepatectomized animals mentioned above and will be further emphasized by our later discussion of the influence of liver damage on the dextrose tolerance curve.

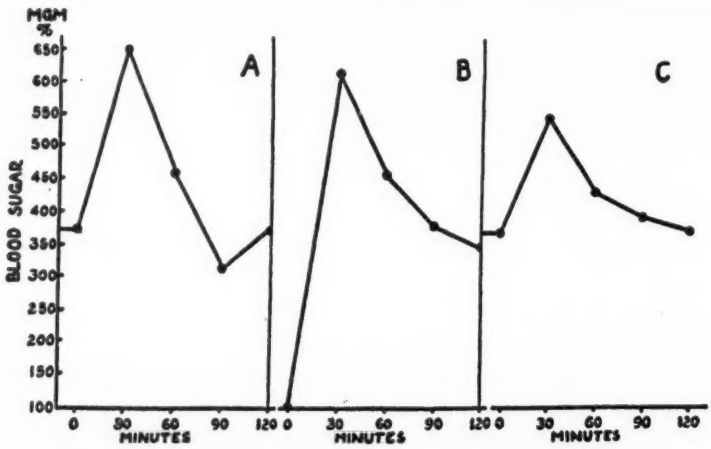

FIG. 2. Dextrose tolerance curves obtained at different times in the same hypophysectomized-depancreatized dog (7), showing the persistence of the blood sugar regulating mechanism of the liver. The threshold of stimulation of the mechanism is elevated, but not to the infinite height to which it is raised in animals with only the pancreas removed. The initial control blood sugars for curves A and C were at the level usually maintained by this animal in the post-absorptive state, when food intake was ample. Prior to the experiment in which curve B was obtained, the animal had been fasted until the blood sugar level fell to 100 mgm. per cent. It may be seen that, except for the initial rapid rise of the blood sugar in curve B, all three curves are strikingly similar. It is evident that the "diabetic" appearance of curve B is due to the fact that the threshold for the homeostatic mechanism did not vary with the initial blood sugar level, but remained fixed by the experimentally altered endocrine balance. Thus the administered sugar in curve B caused an unchecked rise in blood sugar until the threshold value was reached. As soon as this was attained, the normal response of the liver occurred.

INFLUENCE OF THE ANTERIOR PITUITARY GLAND

When the anterior pituitary gland is deficient or absent, as in the hypophysectomized animal, the situation is equivalent to that which would occur if the adjusting screw on the thermostat were turned down as far as it would go so that the furnace would shut off even while the house was cold. This is the significance of the characteristically low blood sugar level maintained in hypopituitarism (6). Conversely, the administration of anterior pituitary extracts will maintain the blood sugar at high levels. In other words, the secretion of the anterior pituitary is a force tending to regulate the blood sugar level in a direction opposite to that of insulin. To revert to our analogy, let us suppose that insulin is represented by a spring tending to pull the thermostat bar towards low temperature regulation and the anterior pituitary secretion is a spring pulling the bar in the opposite direction. Ordinarily the balanced action of both springs keeps the bar floating at the desired normal temperature setting. It will be realized, of course, that the removal of either spring will allow the other one to react violently in the opposite direction. In this connection, consider the marked sensitivity of the hypophysectomized animal to insulin (6). From this

point of view also, it is easy to understand the strong resemblances of hyperinsulinism to hypopituitarism and the high incidence of hyperglycemia or diabetes in hyperpituitarism.

Let us also consider what result one might expect if one were to remove the opposing springs from both sides of the thermostat. The bar would move from its normal point of balance to some other position (depending upon the force of gravity etc.) and regulation would then occur at this fortuitous level. This situation has been duplicated in the living organism by the simultaneous removal of both the pancreas and the pituitary gland (7). Such an animal, when well fed, maintains a blood sugar level in the neighborhood of 350–400 mgm. per cent and yields normal dextrose tolerance curves at that level (fig. 2).

It has been pointed out by analogy that the liver will go through the same regulating process at any level of blood sugar, depending upon where the threshold of the liver is set by the endocrine balance. If this is so the hypophysectomized animal or a hypopituitary human should yield a normal dextrose tolerance curve, except that it will start from a low level and return to the same low level. This is actually the case. But a lack of understanding of all the factors involved has led to misrepresentations of the results obtained, so that the dextrose tolerance curve in hypopituitarism has been variously reported as being abnormally low, normal, and abnormally high.

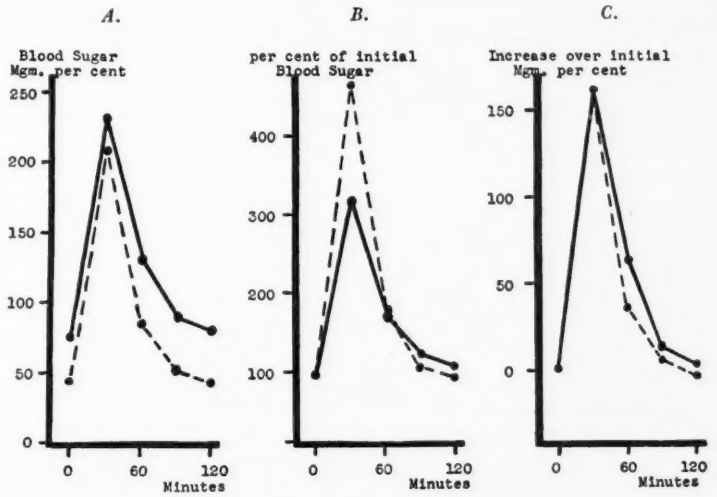

FIG. 3. Intravenous dextrose tolerance tests in a hypophysectomized dog (broken lines) and in a normal dog (continuous lines) compared in different ways:

3A—When absolute values are plotted, the curve of the hypophysectomized animal looks lower than normal.

3B—When percentage increases above initial values are plotted, the curve of the hypophysectomized animal appears to be higher than normal.

3C—When the values are superimposed by plotting absolute increases above initial values, the curves are seen to be practically identical.

Perhaps the most common error leading to the belief that "dextrose tolerance in hypopituitarism is better than normal" has been the administration of the test sugar by mouth. It should be remembered that the low curve obtained by this procedure is a reflection of the diminished rate of absorption from the gastrointestinal tract (8) rather than an index of the ability to handle sugar once it has entered the bloodstream. However, even when the sugar is administered intravenously the apparent tolerance depends upon how the data are expressed.

Figure 3A shows a typical intravenous dextrose tolerance curve in a hypophysectomized dog (broken line) as compared to a similar test in a normal dog (continuous line). The unusual height to which the blood sugar rises and the prolonged return to initial levels (for

intravenous curves) depends upon the fact that an extremely large amount of sugar was used for these tests, namely, 1.75 gm. per kg. body weight. If the lower initial and final levels in the hypophysectomized animal are ignored, its curve appears to be low or better than normal. If, on the other hand, the results of both curves are expressed as percentage rise above the initial level (fig. 3B), the hypophysectomized curve appears to be high or worse than normal. When, however, the actual curves are drawn from the same base-line (fig. 3C) it can be seen that they are practically identical.

THE "TRIPLE TOLERANCE TEST"

Although the principal regulating action of the liver is normal in the hypophysectomized animal, there is a subsidiary regulating mechanism which is not normal, namely, that mechanism which is due to the presence of the pituitary itself. When dextrose tolerance tests are repeated in a normal animal, each test starting as soon as the previous one is over, it will be found that the second curve is lower or better than the first, while the third is usually better than the second. The fourth curve may show some further improvement, but subsequent curves do not. This phenomenon is commonly called the Staub-Traugott effect, after the investigators who first described it (9). Like the dextrose tolerance curve itself, it has been ascribed to the stimulation of insulin secretion from the pancreas, each test being supposed to evoke some excess of insulin so that more is available for the next test. (Why this process does not go on ad infinitum, eventually resulting in hypoglycemia, is not explained.) However, the explanation is obviously not correct in view of the evidence presented above that extra insulin need not be secreted to obtain a normal tolerance curve, and in view of the fact that in those same experiments the Staub-Traugott phenomenon was also demonstrated (2). It has been shown that this phenomenon does not occur in the hypophysectomized animal (10). In the absence of the hypophysis, the first curve is the lowest or best one obtained. It might be supposed that this abnormality is due to some secondary effect of the absence of anterior pituitary secretion upon the function of the liver. But this is not the case, for the administration of anterior pituitary extract to the hypophysectomized animal raises the level of all the tests without restoring the Staub-Traugott phenomenon. The lowering of the

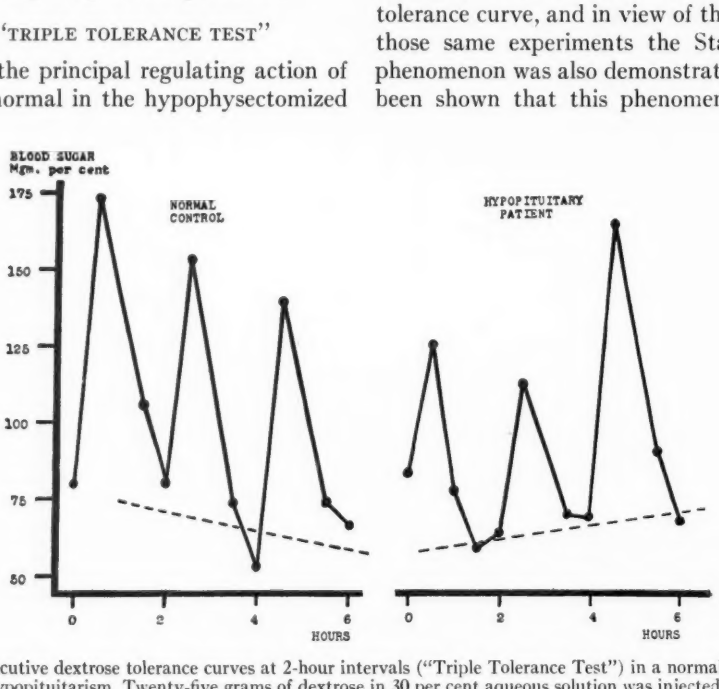

FIG. 4. Consecutive dextrose tolerance curves at 2-hour intervals ("Triple Tolerance Test") in a normal human and in a proven case of hypopituitarism. Twenty-five grams of dextrose in 30 per cent aqueous solution was injected intravenously in every instance. Note the sharp contrast between the slopes of the lowest points in each series, as indicated by the broken lines.

second and third curves (and sometimes the fourth) in the normal animal can therefore best be explained as a *progressive* depression in the activity of the pituitary gland, as a result of repeated or prolonged exposure to hyperglycemic levels. In other words, after several successive doses of sugar the normal animal reaches that stage at which the hypophysectomized animal starts out. This mechanism is very acceptable from the teleologic standpoint, for it is obvious that during continued high sugar intake the regulation will be more efficient as the threshold of the mechanism is lowered. It is equivalent to the common practice of setting down the thermostat of the house to say 50°F. during the spring or fall months when only an occasional, brief cold snap may be expected.

The above phenomenon may be put to clinical use. We have performed consecutive dextrose tolerance tests on humans with proven pituitary dysfunction and obtained results similar to those described for the hypophysectomized dog. Figure 4 compares the curves yielded by such a patient with those of a normal subject. This patient had undergone the surgical removal of a pituitary cyst some 10 years previously and had since presented a variety of signs and symptoms (including marked hypothyroidism) of hypopituitarism. In this patient the first test is quite evidently the best and a line running through the lowest point of each of the three tests would slope *up* to the right. Contrast this with the normal set, where each succeeding test is better than the one before, and a line through the lowest points would slope *down* towards the right. We have called this test the "Triple Tolerance Test" for convenience, and are collecting and expect to publish a series which were done in cases of proven and suspected hypopituitarism. We have found it to be a useful objective criterion when used in conjunction with clinical data.

INFLUENCES OF THE ADRENAL CORTEX AND THE THYROID GLAND

It is difficult at the present time to separate the influences of the adrenal cortex and the thyroid gland on the regulation of the blood sugar from that of the anterior pituitary. Indeed, some of the influence of the anterior pituitary described above may be exerted through these other glands (11, 12). At any rate, deficiency or removal of the adrenal cortex or, conversely, the administration of potent extracts of this gland will lower or raise respectively the blood sugar level in a manner resembling what occurs when the pituitary hormone is varied. To a lesser extent, this is also true of the thyroid (1). Presumably then, the adrenal cortex and the thyroid influence the threshold of regulation of the blood sugar level in the same manner as does the anterior pituitary.

THE ROLE OF THE LIVER

Although we have compared the liver to a thermostat-furnace arrangement, we have thus far considered only those factors which operate by affecting the thermostat part of the mechanism. It is obvious, however, that regardless of where the thermost is set, the state of repair and the capabilities of the furnace will have an important bearing on the degree of regulation which is achieved. For example, a thermostat setting of 80°F. would have no meaning if the furnace were incapable of producing enough heat to raise the temperature of the house to that level. Another consideration is the speed with which the rate of heat production by the furnace can be increased or diminished. Unless such adjustments are rapid, there will be a considerable overswing before the correct temperature is reached. If the thermostat on a sluggish furnace clicks over at let us say 80°F., the temperature may rise to 90 or 100°F. before the effect of shutting off the furnace becomes evident. Finally, even with a furnace of great capacity and high efficiency, the degree of regulation will depend upon the magnitude of the environmental temperature change for which the furnace has to compensate. In other words the usual nightly drop of 10 to 20°F. in the outside temperature might produce practically no perceptible disturbance in the temperature of the house, while a sudden frost dropping the outside temperature 40 to 50° might result in a downward dip in the house temperature before the furnace could cope with it. The analogous con-

siderations apply to the liver as the organ which makes the blood sugar.

An example of a disturbance in sugar regulation, analogous to the situation in which the furnace is incapable of raising the temperature up to the level at which the thermostat is set, is the effect of fasting on the hypophysectomized animal and on the hypopituitary human (13). The withholding of food in the latter organisms results in a progressive hypoglycemia. This does not depend upon any change in regulation because the resumption of food intake immediately restores the previous blood sugar level. It does depend upon a marked reduction in the ability of the liver to make blood sugar from body stores, so that it can not supply sufficient to maintain the blood sugar level unless additional preformed sugar or amino acids regularly enter from the gastro-intestinal tract (14).

The situation in the liver which is analogous to the inadequate furnace, unable to increase or decrease its rates of heat production very readily, is that where the liver is damaged by toxic agents. It is well known that the "diabetic" type of dextrose tolerance curve is obtained in this condition (15, 16).

The "diabetic" type of tolerance curve obtained in starvation or on a high fat diet is analogous to the temporary breakdown in the temperature regulation of the house when a sudden great demand is made upon even a very efficient furnace. Both starvation and fat feeding are alike in that no preformed carbohydrate is being received by the body so that the liver must make all the necessary carbohydrate from its own resources. This represents a high degree of activity on the part of the liver as compared to the normal conditions under which it need manufacture only a small proportion of the body's requirements. The deceleration of sugar output by the liver when sugar is administered requires a longer time when the liver is working at top speed than when it is working at half or quarter speed. The essential correctness of this interpretation is supported by the fact that it is only the first dose of sugar given to a starved or fat-fed animal that results in the "diabetic" type of curve. The second dose (by which time the liver has been able to slow up its production) usually shows a return of the dextrose tolerance curve towards the normal (17).

INFLUENCE OF LIVER DYSFUNCTION ON BLOOD SUGAR REGULATION

In the previous section we described the various ways in which the state of the liver might affect the regulation of the blood sugar level. This may not be of great practical importance when one is dealing clinically with a case of frank liver disease where the danger to life from other consequences of liver failure over-shadows the carbohydrate disturbance. But it may be of considerable value in diagnosis and prognosis when an endocrine disturbance in blood sugar regulation is complicated by the presence of liver dysfunction. Figure 5 illustrates a striking example of this situation. Here we have a pure endocrine disorder, namely, diabetes, resulting from the removal of the pancreas, experimentally complicated by a reversible type of liver damage (18). It will be seen that the characteristics of the diabetes in this dog were markedly changed during the time that the liver was affected (April 1937). The interest of these results is enhanced by the fact that in clinical diabetes mellitus we find two similar types of the disease, namely, the insulin sensitive ("juvenile" or unstable) and the insulin insensitive ("adult" or stable). The depancreatized dog with an unimpaired liver (December, 1936) resembles the individual with insulin-sensitive ("juvenile" or unstable) diabetes mellitus. The morning fasting blood sugar is the highest in the 24 hours; the blood sugar falls sharply during the day under the influence of a dose of insulin with each meal; and then it rises throughout the night hours. In this state the administration of 0.3 units of insulin per kg. body weight causes a quick fall in the blood sugar level of about 200 mgm. per cent. The same animal, which had been on a diet of lean meat, sugar and raw pancreas, was then placed on an equicaloric diet from which the pancreas was omitted. This is known to result in a severe fatty infiltration of the liver (19, 20). The impairment of liver function consequent to the fatty infiltration is reflected in three ways which are characteristic of the insulin-insensitive ("adult" or stable) type of diabetes mellitus (April, 1937). At this

time the diabetes is milder and requires less insulin to control it to a similar degree; the morning fasting blood sugar level is the lowest in the 24 hours; it climbs during the day due to the food intake despite the insulin administered with the meals. The blood sugar then falls during the night hours. The administration of the same amount of insulin as in the previous sensitivity test now results in a much smaller drop in the blood sugar level. The restoration of raw pancreas to the diet of this animal, with a return of the liver function almost to normal (May, 1937), completely reverses the nature of the diabetes to its original condition.

mellitus. Both these procedures will lead to a fatty infiltration of the liver. It should be noted, however, that the diabetes is controlled only at the expense of liver function. Hence it may be said that "the diabetes is better but the patient is worse." The lack of general well-being of patients under those treatments, as compared to patients under modern treatment, may well be ascribed to the difference in the functional state of the liver (21).

THE INTRAVENOUS DEXTROSE TOLERANCE TEST FOR LIVER DYSFUNCTION

The important influence of the state of the liver on blood sugar regulation makes it de-

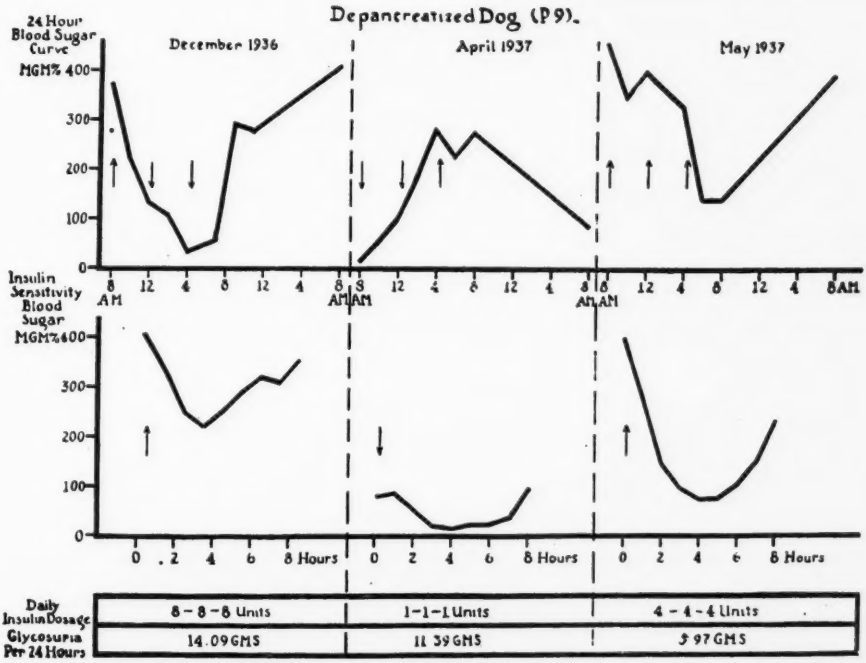

FIG. 5. The influence of the impairment of liver function by fatty infiltration on the characteristics of the diabetic state in a depancreatized dog (18). The fatty liver is present during April 1937 and is caused by substituting meat for the raw pancreas in the diet. Except for this, the food-intake was the same throughout. The arrows in the upper row of curves mark the times of the meals and of insulin administration. The arrows in the lower row of curves mark the injection of 0.3 units of insulin per kg. body weight, in the morning before breakfast, as a test of the sensitivity to insulin.

The above demonstration of the influence of fatty infiltration of the liver on the nature and severity of diabetic manifestations suggests an explanation for the partial success of the extreme high fat diets and starvation regimens formerly used in the treatment of diabetes

sirable to be able to differentiate between hepatic and endocrine disturbances. There have been a number of investigators who have reported that the oral dextrose tolerance curve is abnormal in liver disease, but no characteristics which would distinguish such a curve

from that obtained in diabetes mellitus have ever been described (15, 16). Using a standardized intravenous procedure for the test, my colleagues and I have recently been able to obtain curves from normal individuals, patients with known liver disease and patients with mild diabetes mellitus, respectively, which are characteristic for each condition and which can be differentiated from each other. The procedure, which must be followed exactly if our standards are to be used, is as follows.

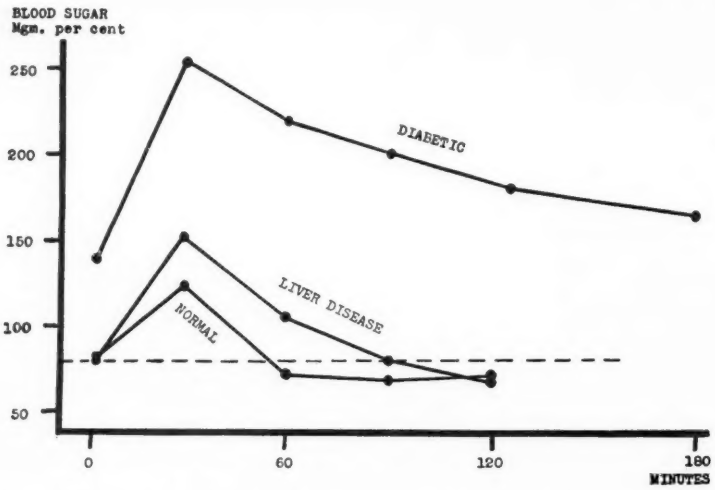

FIG. 6. The average intravenous dextrose tolerance curves of 30 normal control individuals, 25 of the mildest cases of diabetes mellitus which were available and 50 cases of proven mild or early liver disease. The normal curve returns to the pre-injection level by 60 minutes, the hepatic curve returns after 60 and before 120 minutes, the diabetic curve returns after 120 minutes.

The test is done in the morning before breakfast. One-third gram of dextrose per kg. body weight, in a 50 per cent aqueous solution, is injected intravenously within a period of 3 to 5 minutes. Blood samples are taken before the sugar administration, and at $\frac{1}{2}$, 1 and 2 hours thereafter. We used arterial blood obtained by finger puncture and the micro modification of the Somogyi-Shaffer-Hartmann method for true blood sugar.

Figure 6 shows the average curves for 30 normal control individuals, 25 of the mildest cases of diabetes mellitus which were available to us (none had a fasting blood sugar level over 200 mg. and none required insulin for the control of their diabetes) and 50 cases of mild or early liver disease (clinically established and corroborated by several laboratory criteria). The wide spread between the 3 types of curves and the ease with which they can be differentiated are apparent. As regards the variation among the individual tests which go to make up the average curves, not one of the 30 normal subjects took as long as 60 minutes to return to the pre-injection level (this agrees with the normal standard previously reported by Tunbridge and Allibone (22)), none of the 25 cases of mild diabetes took less than 120 minutes to return to the initial level and, of the 50 cases of mild or early liver disease, none took as long as 120 minutes to return to the pre-injection level, although 13 of the 50, or approximately 25 per cent, did cross the baseline in less than 60 minutes.

It might appear at first glance from the average curves, that the differentiation between the diabetic and hepatic type can just as readily be made from the higher initial level, and the higher peak value of the former. This is not so when individual curves are considered. The characteristics of the average curves depend upon the fact that more of the diabetic curves started at and reached higher levels. However, the range of these values in diabetes and in liver disease actually over-

lapped to some extent. Figure 7 shows that when this was the case, the characteristic downward slope of the curve and the time at which it crossed the base-line were the real differentiating factors. The curves in figure 7 are for individual cases of diabetes and of liver disease, selected because they happened to start at identical fasting blood sugar levels. It may be seen that, while the initial levels and highest peaks did not distinguish between the two conditions, the characteristic downslope and time of return to the pre-injection level permitted easy distinction. The detailed data upon which this useful clinical test is based will appear in a forthcoming publication (23).

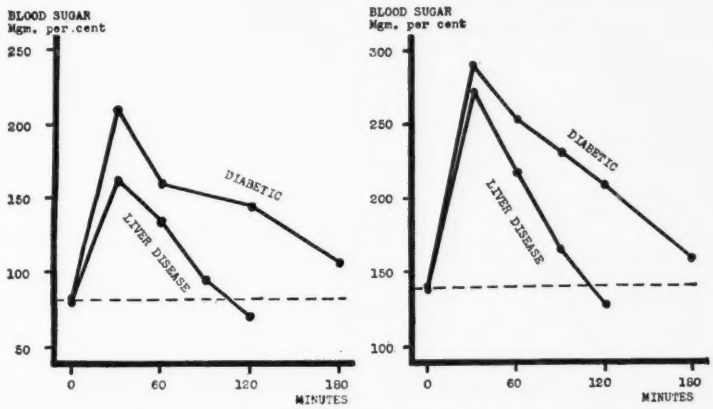

FIG. 7. Individual intravenous dextrose tolerance curves in cases of diabetes and of liver disease, which happened to start at identical fasting blood sugar levels. The characteristic downslopes and times of return to the pre-injection levels are the criteria for differentiation.

ACTUAL COMPLEXITY OF REGULATION IN THE LIVING ORGANISM

Thus far the analogy of the thermostat-furnace arrangement has served us well in helping to simplify the relationship between the endocrine glands and the liver in the regulation of the blood sugar. But, before proceeding to a consideration of the clinical disturbances in blood sugar regulation, it is necessary to realize that the mechanism which has been described is integrated with a series of other regulatory processes in the body. We have said, for example, that the threshold of regulation of the liver is determined by the endocrine balance. But what determines the characteristic rates of activity of the endocrines which compose this balance? This question cannot be answered at the present time, although we do have some hints concerning certain factors. Thus we have already cited evidence which indicates that the blood sugar level affects not only the liver but also the activity of the anterior pituitary gland, which in turn, influences the reaction of the liver to the blood sugar level (10). There is also evidence that the concentration of sugar in the blood passing through the pancreas influences the rate of secretion of insulin (24). Furthermore, the concentration of a given hormone in the blood may have a controlling action upon the activity of the gland which secretes that hormone (25). Another mode of regulation may occur by the controlling effect of the hormone of one gland upon the rate of activity of another gland. An example of the latter type of effect is the excessive stimulation of the secretion of insulin by the repeated injection of massive doses of extracts of the anterior pituitary gland, eventually leading to islet exhaustion and pancreatic diabetes, as first described by Young (26, 27).

It is not unusual in the study of biologic functions to find a number of overlapping mechanisms all directed toward the same end and each capable of serving the function to a considerable extent when the other mechanisms are impaired by disease or by an experimental procedure. This situation exists in regard to

the regulation of the blood sugar. It has been possible to demonstrate a primitive type of regulation of sugar output by the liver, which can occur in isolated hepatic tissue in the test-tube (28). If, under the proper experimental conditions, the rate of appearance of free sugar in isolated minced liver is followed at short intervals, that rate will be diminished proportionately to the concentration of a sugar solution added to the liver mince at the beginning of the experiment. In other words, the output of sugar is to a certain extent controlled by the concentration of sugar present, even in the absence of any possible endocrine adjustment. In addition to this intrinsic hepatic mechanism and its endocrine regulators which have already been discussed, there are also certain emergency mechanisms mediated by the central nervous system and the adrenal medulla (1). The latter mechanisms do not operate under normal conditions for they can be entirely eliminated experimentally without appreciably affecting the sensitivity of regulation. But when, under abnormal conditions of stress and strain, the organism is threatened by an unduly rapid or profound hypoglycemia, the emergency mechanisms rapidly come into play by breaking down liver glycogen and providing the needed blood sugar.

It may be helpful to think of the relationships between all the regulatory mechanisms from the standpoint of evolutionary development. The fundamental or primitive regulation may be supposed to reside in the biochemical processes of the tissue cells themselves. The endocrine glands may represent a step up the evolutionary scale by providing a more sensitive and more adjustable regulating mechanism, which renders the more highly developed organism less dependent upon its external environment. The emergency mechanisms may be regarded as an additional protection against hypoglycemia for the central nervous system of the most highly developed organisms.

CLINICAL DISTURBANCES IN THE ENDOCRINE REGULATION OF THE BLOOD SUGAR

Having outlined the influences of the various endocrine glands upon the process of regulation which occurs primarily in the liver, it becomes a simple matter to account for the characteristic clinical disturbances in regulation which accompany disease or dysfunction of the glands or the liver. But in order to avoid confusion in terminology, it is necessary to remember at the outset that diabetes mellitus is still a clinical syndrome of unknown etiology. The essential and minimal characteristics of this syndrome are a persistent hyperglycemia with glycosuria, all other effects such as polyuria, polydipsia, dehydration, demineralization, loss of weight, ketosis and coma being secondary (1). In the mildest disturbances the diagnosis of diabetes mellitus often cannot be finally established until the condition has progressed in severity to the point that stable, persistent criteria develop. It often happens also that a mild disturbance in carbohydrate regulation is found to be accompanied by hepatic damage, hyperthyroidism, adrenal cortical tumor, etc. If the liver disease or the glandular disturbance is adequately treated by medical or surgical means and the carbohydrate disturbance is thereby eliminated, it is not customary to label the transitory hyperglycemia and glycosuria as diabetes mellitus.

It is readily understood that the above terminology is merely a clinical convention. From the physiologic standpoint it is difficult to conceive of a disturbance like diabetes mellitus which, in some individuals, would not be found in minimal and transitory form. Nor does the presence of frank and remediable liver disease or glandular disturbance necessarily make the resulting diabetes any different from that which occurs when the etiologic disturbance cannot be detected by present clinical methods. It is this physiologic point of view which must be kept in mind in considering the possible etiologic factors involved in the recognized clinical disturbance.

Since the condition, which by clinical convention is called diabetes mellitus, is characterized at the present time by the very lack of any consistent demonstrable abnormality in the endocrine glands, we must perforce base our notions as to possible etiology upon the various experimental procedures by which a similar syndrome can be produced. These possibilities have already been indicated in the sections devoted to the various endocrine

glands and the liver. Their relationships to each other are graphically illustrated in figure 8. In the balance of forces represented there, it may be readily seen that the same end-result might be obtained in a variety of ways. A shift of regulation towards hyperglycemia might be due to a diminution in the insulin factor (an absolute lack of insulin), or to an intensification of the opposing factors (a relative lack of insulin). If the latter type of disturbance is indeed responsible for some cases of diabetes mellitus it is possible that we may eventually learn to distinguish a pituitary

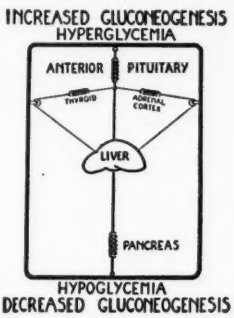

FIG. 8. Mechanical analogy to the endocrine balance, as it affects the regulation of the blood sugar by the liver.

diabetes, an adrenal cortical diabetes and a thyroid diabetes, as well as pancreatic diabetes. To this list must be added a possible hepatic diabetes which might occur in the absence of endocrine disturbance, when the liver is no longer responding normally to its endocrine regulation. *It must be emphasized that none of these considerations minimizes the importance of insulin in therapy, or suggests that any other efficacious agent is known at the present time.* The diagram clearly indicates that the important thing from the therapeutic standpoint is the maintenance of the normal balance. The administration of insulin will correct the imbalance whether it is due to an absolute or a relative lack of this hormone.

The differentiation of the various possible types of diabetes mellitus must await the development of adequate methods for the quantitative estimation of glandular function or of the titer of the various hormones in the blood. For the present, all diabetic manifestations which are accompanied by a clinically recognizable dysfunction of some gland or of the liver are considered to be part of the syndrome associated with that clinical state. A similar situation exists as regards carbohydrate disturbances in the direction of hypoglycemia and the differentiation between hyperinsulinism and other conditions which may lead to hypoglycemia. An inspection of the following list in conjunction with figure 8 will relate the characteristic blood sugar disturbances accompanying the various known endocrine syndromes with the physiologic considerations which have been outlined. We have included key references to articles dealing with the carbohydrate disturbance in the clinical syndrome.

ENDOCRINE HYPERGLYCEMIAS

Anterior Pituitary—Acromegaly (29)
—Pituitary basophilism (30, 31)
Thyroid—Hyperthyroidism (32)
Adrenal Cortex—Adrenogenital syndrome (30, 31)
Adrenal Medulla—Pheochromocytoma (33)
Pancreas—Diabetes mellitus, in those cases where there is evidence of the absence or destruction of the Islets of Langerhans (34)

ENDOCRINE HYPOGLYCEMIAS

Anterior Pituitary—Simmonds' disease (35)
—Anorexia nervosa (36)
Thyroid—Hypothyroidism (37)
Adrenal Cortex—Addison's disease (38)
—Adrenal apoplexy (39)
Pancreas—Hyperinsulinism (40)

SUMMARY

In the foregoing review the following subjects were considered: the homeostatic mechanism of the liver; the influence of the pancreas; the role of the anterior hypophysis; the triple glucose tolerance test for the diagnosis of hypopituitarism; the influence of the adrenal cortex and the thyroid; liver dysfunction and blood sugar regulation; the intravenous glucose tolerance test for liver dysfunction; the complexity of regulation in the living organism; and clinical disturbances in the endocrine regulation of the blood sugar.

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ASSOCIATION NOTICE

The Twenty-Seventh Annual Meeting of The Association for the Study of Internal Secretions will be held in Chicago, Illinois, on Monday, June 12, and Tuesday, June 13, 1944. The Stevens Hotel will be the headquarters for registration and for the scientific and business sessions. Room reservations should be made directly with the Stevens Hotel. Hotel and transportation reservations should be made immediately.

The Chairman of the Local Committee is Dr. Willard O. Thompson, 700 North Michigan Avenue, Chicago.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. D. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, HAROLD WOOSTER.

ENDOCRINE GENERAL

CHAIKOFF, I. L., C. ENTENMAN, J. F. RINEHART AND F. L. REICHERT

Development of cirrhosis in the liver of dogs deprived of both pituitary and thyroid glands. *Proc. Soc. Exp. Biol. & Med.* 54: 170. 1943.

The livers of 9 dogs were examined at intervals of 70 to 419 days after they had been deprived of both pituitary and thyroid glands. A fatty infiltration of the liver was observed in 8 of them. The livers of 6 contained abnormal amounts of fibrosis tissue. All degrees of cirrhosis from early to advanced portal cirrhosis were found. The high fat content (11 to 52%; average 21%) suggested that a fatty infiltration preceded the formation of fibrous tissue in the liver of the dog.

Cirrhosis of the liver was not observed in dogs subjected to thyroidectomy alone but in these animals the fat content of the liver did not exceed 11%.—*C.W.T.*

CORNER, G. W., SR.

Tropic versus trophic in the terminology of the pituitary hormones. *Endocrinoly.* 33: 405. 1944.

The writer presents the etymological basis in favor of the adjectival suffix "trophic" rather than "tropic" and of the noun form "trophin" as opposed to "trophe." His authoritative discussion should be helpful in promoting uniformity and correctness in usage.—*H.O.H.*

DEANESLY, R., AND A. S. PARKES

Deposition of protein material in implanted pellets of steroid hormones. *Lancet* 245: 500. 1943.

Compressed tablets of estradiol, progesterone, testosterone and desoxycorticosterone acetate are absorbed from subcutaneous tissue at about the same rate as fused blocks of these agents. A meshwork of protein material is deposited throughout the tablets, but is superficial on the blocks. No evidence of living tissue in the meshwork or histologic connection with the connective tissue capsule about the pellets was found. The meshwork appears before encapsulation with connective tissue occurs, and so is not dependent on the latter. The meshwork does not slow absorption of the steroids.—*Courtesy Biol. Absts.*

FARMER, L.

Effect of follicular hormone on anaphylactic shock. *Proc. Soc. Exp. Biol. & Med.* 54: 5. 1943.

Contrary to the report of Schafer (Med. Klin., 1937, *33*, 1061) it was observed that administration of alpha-estradiol to serum-sensitized female guinea pigs did not enhance their anaphylactic response.—*C.W.T.*

FLAVELL, G.

Webbing of the neck, with Turner's syndrome in the male. *Brit. J. Surg.* 31: 150. 1943.

A case displaying all of the classical requirements of Turner's syndrome (Endocrinology, 23: 566, 1938) except that the patient was a male, was described. Examination of the 21-year-old male revealed webbing of the neck, cubitus valgus, some kypho-scoliosis with prominence of the sternum, third-degree bilateral claw-feet (a feature not described previously in such cases), scanty beard, absence of chest hair, almost complete absence of axillary hair, female distribution of pubic hair, wide hips, normal penis, testicles about one-third normal size. The patient, married three months, stated that erections and emissions were normal. Radiographs of the cervical region showed a failure of union of the fifth cervical neural arch in the midline but no other abnormalities. There was no limitation of movement of

the neck except the slight constraint resulting from the webs themselves and there was nowhere any evidence of neurological change. The author considered of some significance the fact that the patient's father had an infantile left hand. The possibility that this syndrome results from a foetal developmental failure rather than from pituitary dysfunction, as suggested by Turner, was discussed.—*D.P.*

GORDON, A. S., F. J. TORNETTA AND H. A. CHARIPPER

Effect of low atmospheric pressures on reproductive system of the male rat. *Proc. Soc. Exp. Biol. and Med.* 53: 6. 1943.

Adult male rats weighing 200–280 gm. were exposed to pressures of 280–250 mm. Hg. equal to 25,000 to 28,000 feet altitude 6 hours daily for 14 to 18 days. Examination of sections of the testes showed marked degeneration of the spermatogenic cells. The tubular lumina were devoid of sperm. The interstitial tissue of the testis and epithelium of the seminal vesicle and prostate gland, however, appeared only slightly atrophied. Pituitary glands displayed increases in the numbers of basophiles. Assay of the pituitaries showed increased amounts of gonadotropic hormone. The degenerative changes described in the male gonad are believed to be due to a direct inhibitory action of the low atmospheric pressures on the germinal tissue of the testis. The histological and gonadotropic hormone content changes in the pituitary probably represent a reflection of this inhibition.—*C.W.T.*

GUIMARAES, J. R. A.

Treatment of ulcers of the lower extremities. *Arq. Dermat. e Sifilogr. Sao Paulo* 6: 65. 1942.

Local and parenteral treatment with estrone, estradiol, estradiol dipropionate or testosterone rapidly cured crural ulcers. Six case reports are presented and illustrated.—*Courtesy Biol. Absts.*

LYONS, WM. R.

Pregnancy maintenance in hypophysectomized-oöphorectomized rats injected with estrone and progesterone. *Proc. Soc. Exp. Biol. & Med.* 54: 65. 1943.

It has been shown that pregnancy is quickly terminated in the rat if hypophysectomy is performed before day 11. In the present experiment rats oöphorectomized and hypophysectomized on day 7 or 8 of pregnancy, when administered daily 1 mg. of estrone and 3 or 4 mg. of progesterone were able to carry the majority of the fetuses to term. It is suggested that the pituitary's main role in the first half of pregnancy is to secrete 3 hormones (FSH, ICSH and lactogenic) which cause the ovaries to form daily equivalents of 1 mg. of estrone and 3–4 mg. of progesterone.—*C.W.T.*

MULLIGAN, R. M.

Hair loss in male dogs fed stilbestrol. *Proc. Soc. Exp. Biol. & Med.* 54: 21. 1943.

The peroral administration of stilbestrol over several months to male dogs caused losses of hair in various regions of the body and failure of hair regeneration in clipped areas. It was suggested that a similar phenomenon might be anticipated in man.—*C.W.T.*

NORMAN, F. A., AND G. J. FASHENA

Chronic hypergalactosemia. *Am. J. Dis. Child.* 66: 531. 1943.

The authors report the history of a male infant of 11 weeks who developed recurrent episodes of projectile vomiting and weight loss. He was found to have chronic hypergalactosemia associated with galactosuria, albuminaria, nutritional disturbance, hepatosplenomegaly, anemia, mild azotemia and osteoporosis. Removal of milk from the diet resulted in disappearance of all symptoms except azotemia. The essential disturbance is thought to be an inborn error in metabolism involving the specific enzyme system concerned with the conversion of galactose to glycogen. Since this mechanism can not act efficiently on galactose it acts exclusively on dextrose, thus filling the liver with glycogen and keeping the blood dextrose level at low starvation levels. This is the third case of this disorder to be reported in the literature.—*E.C.R., Jr.*

SELKURT, E. E., L. J. TALBOT AND C. R. HOUCK

Effects of estradiol on urinary excretion of ascorbic acid in the dog. *Proc. Soc. Exp. Biol. & Med.* 53: 96. 1943.

An investigation was made of the effect of the estrogen, estradiol-benzoate, on the urinary excretion of ascorbic acid by the dog, an animal capable of synthesizing ascorbic acid. The effects of the injection of estradiol became apparent in 3 or 4 days by a rise in the daily excretion of ascorbic acid, by a decrease in tubular reabsorption, and by a rise in the ascorbic acid clearance/creatinine clearance ratio. As a result, the fasting plasma levels of ascorbic acid fall during the treatment.—*C.W.T.*

SMITHCORS, J. F., AND S. L. LEONARD

Limited effects of certain steroid hormones on mammary glands of hypophysectomized rats. *Proc. Soc. Exp. Biol. & Med.* 54: 109. 1943.

Hypophysectomized rats were treated immediately or 4 to 8 days later with progesterone alone or in combination with estrogen and with desoxycorticosterone acetate. The mammary glands of these animals were stimulated with progesterone and estrogen alone or in combination only when treatment was begun immediately. Desoxycorticosterone was ineffective. These studies emphasize the necessity of adequate pituitary hormones to produce a fully developed mammary gland.—*C.W.T.*

GONADS

DVOSKIN, S.

Local maintenance of spermatogenesis in hypophysectomized rats with low dosages of testosterone from intratesticular pellets. *Proc. Soc. Exp. Biol. & Med.* 54: 111. 1943.

Very small dosages of testosterone, administered intratesticularly to hypophysectomized rats, cause a regional maintenance of spermatogenesis. These dosages are much less than those necessary for complete maintenance of the sexual accessory glands. Testosterone is believed to have a direct action on the testes in the maintenance of spermatogenesis.—*C.W.T.*

HARDING, F. E.

Treatment of cryptorchidism. Report on treatment in thirty-eight cases with chorionic and pituitary gonadotropin and testosterone. *J. Ped.* 23: 45. 1943.

The author treated 38 cases of cryptorchidism with varying amounts of chorionic gonadotropin, testosterone, and pituitary gonadotropin. Descent occurred in 76 per cent of cases following from one to 28 weeks of therapy; failure of descent was diagnosed after 4 weeks of therapy. The author reviews the literature. He states that cryptorchidism without mechanical obstruction may be corrected with hormonal therapy. Prognosis varies, since it is impossible to diagnose obstruction and since the number of patients with obstruction varies. Hormonal treatment aids in the early diagnosis of obstruction, so that surgery can be performed to prevent psychic trauma, sterility, hypogonadism and possibly malignant degeneration. Treatment with hormones lengthens the spermatic cord and enlarges the scrotum and testes thus facilitating operation. In the series reported, there was no harm to the testes that could be detected, regardless of the age at which the boy was treated.—*E.C.R. Jr.*

RHODES, A.

Pseudohermaphoditism in twins. *Arch. Ped.* 60: 529. 1943.

The author observed twin infants aged 7 weeks with: 1) anterior penis-like organs about 20 mm. long bound down with adhesions, 2) folds of skin resembling labia majorae, 3) external urethral orifice at the base of the penil organ, 4) small dimples lined with mucous membranes posterior to the urethral opening, and 5) no palpable gonads. He guessed that they were male external pseudohermaphrodites with perineal hypospadias, bifid scrotum and failure of the descent of the testes. Their course is being followed. The author cites in detail the eight previously reported cases in the literature.—*E.C.R., Jr.*

WELLS, L. J.

Descent of the testis: anatomical and hormonal considerations. *Surgery* 14: 436. 1943.

In this comprehensive review of the literature relating to descent of the testis, anatomical and hormonal considerations and the present status of the problem are discussed. The following conclusions were drawn. 1. Some observations suggest that in man hormones (chorionic gonadotropin and androgenic substances) are related to normal, prenatal descent of the testis. However, the capacity of fetal organs to respond to available hormones deserves additional investigation. 2. In certain species, hypophyseal gonadotropins and androgen influence normal, puberal descent. 3. It appears that estrogen does not favor normal descent. 4. If, in man, "unilaterally undescended testes" descend spontaneously several years after birth, the question arises as to how hormones (equally distributed to both sides of the body) could influence the prenatal descent of one testis and not of the other. 5. It is unlikely that the gubernaculum pulls the testis into the scrotum. 6. It is questionable whether the gubernaculum penetrates the external spermatic fascia and attaches to the scrotum. 7. The inguinal cone probably has little or no influence upon descent of the human testis. 8. Factors causing the formation of the inguinal bursae (Klaatsch) are unknown.—*D.P.*

HYPOPHYSIS

MARX, W., E. ANDERSON, C. T. O. FONG AND H. M. EVANS

Effects of growth hormone on glycosuria of fed partially depancreatized rats. *Proc. Soc. Exp. Biol. & Med.* 53: 38. 1943.

Although it has been well established that the secretions of the anterior pituitary profoundly influence carbohydrate metabolism, it has not been shown as yet which hormone or hormones are involved in this relationship. A growth hormone extract which was practically free of lactogenic, adrenocorticotropic, thyrotropic and gonadotropic hormones was administered to partially depancreatized rats fed a 20% sucrose solution as their only food and drink. The hormone was given once daily for 3 days at levels varying from 1.5 to 15.0 mg. total dose. A marked increase in glucose excretion was observed on the third day of injection as compared to the preinjection level on the same feeding plan.—*C.W.T.*

PASQUALINI, R. Q., AND A. AVOGADRO

Action of pitressin on thirst in patients with diabetes insipidus. *Rev. Soc. argent. biol.* 18: 88. 1942.

Two cases of diabetes insipidus were deprived of water for several hours. When thirst became intense 5 u. of Pitressin in oil was injected. Thirst disappeared in 20 minutes, although no water was given. It is suggested that pitressin has other effects besides its well known antidiuretic activity.—*Courtesy Biol. Absts.*

STRAUSS, A. A., AND E. H. WATSON

Studies in hormone therapy. I. The evaluation of growth hormone treatment. *J. Ped.* 23: 421. 1943.

The authors have been treating for some years a group of mentally defective children with a preparation of anterior pituitary growth hormone. In this paper they report 3 methods by which they are evaluating the results of this therapy: 1) by plotting the height curve against the chronological age line; 2) by tabulating the increment in height age (in month values) over regular six-month periods; and 3) by using a height ratio (height quotient). The modification of growth induced by this preparation will be reported subsequently.—*E.C.R., Jr.*

PANCREAS

DRAGSTEDT, L. R.

Some physiologic problems in surgery of the pancreas. *Ann. Surg.* 118: 576. 1943.

Experimental work carried out in the author's laboratory and elsewhere on various aspects of pancreas physiology were reviewed. The following impressions gained from work on experimental animals, chiefly the dog, were suggested as a guide in the clinical problem of surgery of the pancreas. 1. Removal of from 80% to 90% of the pancreas causes no defect in carbohydrate or fat metabolism or in the digestion and absorption of food-stuffs, provided the pancreas remnant remains in connection with the duct and its secretion has free access to the upper intestine. 2. Removal of from 90% to 95% of the pancreas, leaving the remnant attached to the duct, produces a diabetes, characterized by marked hyperglycemia and glycosuria, excessive insulin requirement, and hyperlipemia. Digestion and absorption are unimpaired. Lipocaic is usually required. 3. Complete pancreatectomy produces a diabetes less severe but more difficult to control. Hyperglycemia and glycosuria are not so marked and less insulin is required. Hypolipemia develops and lipocaic is almost always needed. Moderate to severe impairment in the digestion and absorption of fat and protein may be expected. The absorption of carbohydrate is little affected. 4. Permanent occlusion of the pancreatic ducts produces a similar impairment in digestion and absorption. Atrophy of the pancreas results. If partial pancreatectomy has also been performed the atrophied remnant of pancreas becomes deficient as an endocrine organ and varying degrees of lipocaic deficiency and diabetes appear. Hypolipemia becomes pronounced. 5. Present information does not indicate that any specific defect will result from removal of the duodenum, but patients who survive for long periods after this operation should be observed carefully for the possible development of pernicious anemia. It was emphasized that the better nutritive state displayed by animals in which a remnant of pancreas, however small, is left in connection with its duct, as compared with those in which the ducts are occluded or the entire pancreas removed, suggests that this should be attempted whenever possible and a simple procedure used in the dog was described and illustrated. With respect to substitution therapy, pancreatin has proved partially effective in man but in the dog

fresh raw pancreas has always yielded the best results.—*From Author's Summary.*

ROCKEY, E. W.

Total pancreatectomy for carcinoma. *Ann. Surg.* 118: 603. 1943.

A case of carcinoma of the pancreas, with total pancreatectomy was described, including postmortem findings. The insulin requirement did not reach the anticipated level. Death from chemical peritonitis (bile) occurred 15 days after operation. There were no fatty changes in the liver in the two-week period. Suggestions for the management of similar cases were offered. It was emphasized that frequent blood sugar determinations are essential to avoid hypoglycemia.—*D.P.*

PARATHYROID

STOERK, H. C.

Activity of parathyroid hormone in the nephrectomized rat. *Proc. Soc. Exp. Biol. & Med.* 54: 50. 1943.

It was reported that within 48 hours, parathyroidectomy lowered the serum Ca in nonnephrectomized mature rats from 10.7 to 8.3 mg.%. In the same period of time Ca in nephrectomized-parathyroidectomized rats decreased from 9.5 to 6.5 mg.%. The injection of 5×20 units of parathyroid extract (PTH) into normal rats, after 48 hours produced an average elevation of the serum Ca of 1.5 mg.%. The injection of the same quantity of PTH into parathyroidectomized-nephrectomized rats, after the same time produced an average elevation of the serum Ca of 4 mg.% (from 6.5–10.5 mg.%). These experiments indicate that PTH raises the blood Ca without the intermediation of the kidneys. They do not exclude the possibility, however, that the hormone may, under normal conditions, also affect renal function.—*C.W.T.*

THYROID

BRONSTEIN, I. P., L. E. BOWER AND J. MURPHY

Familial cretinism. Two brothers exhibiting thyroid deficiency and epiphyseal dysgenesis. *Am. J. M. Sc.* 205: 114. 1943.

Familial cretinism is rare in this country. Two brothers exhibited the following classical symptoms which readily identified them as cretins: dwarfed stature, mental inadequacy, supraclavicular fat pads, macroglossis, large abdomen and dry skin. Roentgenograms of the bones revealed marked retardation of skeletal growth with fragmentation and stippling of the epiphyses of the humeri and femori. A biopsy of a supraclavicular fat pad was obtained in one case. Improvement followed in both patients upon the administration of thyroid extract.—*Courtesy Biol. Absts.*

GOETSCH, EMIL

A new concept regarding the origin of so-called primary carcinoma of the hyperplastic thyroid. *Ann. Surg.* 118: 843. 1943.

Nine instances of incipient carcinomatous lesions occurring in the diffuse hyperplastic thyroid were studied. In three of these cases, two of which were described in detail, the carcinomatous nodule showed a central minute cancerous adenoma. In several of the remaining cases, the origin of the malignant lesions in preexisting minute adenomata was strongly suspected. These findings were presented as evidence that carcinoma apparently primary in (exophthalmic) hyperplastic goiter is, in fact, secondary to malignant degeneration of an intermediate preexisting minute adenoma. It was concluded that 1) the concept of primary carcinoma occurring in the hyperplastic thyroid is not based on firm premises and 2) probably carcinoma is rarely, if ever, truly primary in the hyperplastic thyroid gland.—*D.P.*